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**A model to study the flow and use of knowledge in  
Outsourced Knowledge Intensive projects: A multi-  
case study of three vaccine clinical trials in Latin  
America**

**Countries researched: Colombia, Brazil and Mexico**

Sara Marcela Valencia Cadavid

Ph.D., Science and Technology Studies

University of Edinburgh

2018

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# Abstract

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This thesis offers insights from knowledge management theory to understand the flow of knowledge across the multiple actors involved in the execution of a clinical trial in Latin America. In the last 12 years, the participation of Latin America in the business of clinical trials has significantly increased, becoming a highly demanded region to implement sponsored clinical research, overtaking regions like Africa, India, Southeast Asia, and Middle Eastern countries. Also, over this period, sponsors have increased the outsourcing of in-house activities such as trial monitoring, pharmacovigilance and regulatory services to Contracted Research Organisations (CROs), shifting the ‘two organisations’ and bi-directional relationship between the sponsor and the research sites. This change in the clinical trials landscape has also taken place in Latin America, where in addition to the CRO, the figure of Site Management Organisations (SMOs) has emerged to manage multiple research sites over the course of the trial. Therefore, the internationalisation of clinical research, plus the outsourcing of strategic activities, have transformed the implementation of clinical trials in the region.

On the other hand, the results of a clinical trial depend strongly on the analytical skills and cognitive capabilities employed by people working on the project. These characteristics make the clinical trial a Knowledge Intensive Project (KIP), where the main project outcomes depend to a large extent on the use of knowledge by the workers, and the transfer of knowledge data and information across the multiple organisations working in the clinical trial. Because knowledge is the primary production factor in a clinical trial, and in the context of Latin America, to my knowledge, there is reduced research about the production of clinical evidence and the role of each one of the actors over the execution, the main research question that this thesis answers is: *How does knowledge flow across organisations and is employed by people in their firms to implement the clinical trials and obtain their respective results?*

To answer this research question, I proposed and evaluated a three-step model to study the flow of knowledge, data and information across multiple organisations being part of the clinical trial and the use of these to produce the knowledge products by the

sponsor and the research sites. This model has its roots in the literature of knowledge 'models, work and processes', the concept of interdependence and the literature of knowledge transfer and acquisition in the outsourced project. The model consists of three steps to address, at the inter-organisational level, the transfer and acquisition of knowledge, data and information and the interdependency on results; and at the intra-organisational level, the use of knowledge and storage. The presented model was evaluated and complemented based on the evidence collected through a multi-case study of three multi-organisational clinical trials to evaluate three new vaccine candidates in Colombia, Brazil and Mexico.

The findings of this research indicated that the model was robust to study the flow of knowledge, data and information between the sponsor and the research sites, from the design of the protocol to the production of the clinical data. The results also indicate that the presence of intermediaries decreases the transfer of knowledge and information between the parts, and induces the selectivity of the research sites toward one of the sources of knowledge, the Sponsor, the CROs or SMO. The evidence shows that the acquisition of knowledge by physicians demands a knowledge-destruction capability to actively employ the acquired knowledge in the trial and the constant presence of loops to reinforce the knowledge acquisition. The empirical findings of knowledge and data acquisition by the research sites and the sponsor contributed to developing the concept of permeability, contributing to the literature of knowledge acquisition in outsourced projects. This research addresses, for the first time, the implementation of vaccine clinical trials in Latin America countries and the contribution of the local researcher to the project, especially with their knowledge about the communities intervened. But it also highlighted some of the aspects that affect the implementation of clinical trials, such as the labour conditions in academia, which induce turnover, and the lack of harmonisation among clinical trial regulation in the region. In conclusion, the model proposed allowed me to address simply the complexities that take place in the production of knowledge products in multi-organisational clinical trials in Latin America countries.

## Lay summary

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One of the aims of this research is to study Latin America because of the strong participation of the region in the business of clinical trials and the changing landscape of this kind of projects over the last years. Clinical trials used to have the participation of two organisations. Now the number of firms has increased, making the operation of these projects more complex. The participation of organizations such as CRO (Contracted Research Organisation) and Site Management Organisations (SMOs) are changing the implementation of the clinical trials. The change in the implementation motivated the proposal of this research in the first place.

The main objective of this thesis is to study how across multiple firms working on clinical trials deliver results that each firm produced. Likewise, how these firms share and use those results with their partners, and how those results become products. In the context of this research, a clinical trial is defined as a knowledge-intensive project because the strong demand of analytical skills required to produce the results, and these results, in turn, are denominated productive enquiries. To my knowledge the research on this topic is limited, therefore the main research question that emerged is: *How does knowledge flow across organisations and is employed by people in their firms to implement the clinical trials and obtain their respective results?* The theory employed to study this “knowledge flow” is from knowledge management theory because it allows to pay attention exclusively to the use and production of knowledge over the course of the entire project. Using this theory, I propose and evaluate a conceptual model to answer this research question. The model is divided into three main steps: knowledge acquisition, knowledge use and knowledge transfer/storage. The concepts of interdependence and the literature of knowledge transfer and acquisition in outsourced projects are also employed in the model proposed. The presented model is evaluated and complemented based on the evidence collected through a multi-case study of three multi-organisational clinical trials to evaluate three new vaccine candidates in Colombia, Brazil and Mexico.

The results of this research provide evidence that indicates that the theoretical model proposed is strong enough to study the complexities on the flow of knowledge across multiple firms working in a clinical trial. This model covered from the beginning of the project design until its production of clinical data, more data is required to study the production of the final product. One of the main outcomes of this project was the identification of intermediaries transferring information and knowledge and how they affected this process. The presence of these actors led place to a reaction from the receptor that I denominated selectivity, a reaction that is associated with a concept developed in this thesis that is permeability. In those cases, in which more than two sources transferred information, the receptor becomes more or less open to one of the sources. In other words, the receptor was more or less permeable to receive and use one of the sources information. Another significant finding of this work is the process of re-learning by experienced physicians to produce clinical data. This process is named in the literature as knowledge-destruction capability which had to be actively employed by experienced physicians to de-learn old practices and learn how to produce clinical data in the context of clinical research. This process required a constant communication with external sources to verify the validity of the new knowledge acquired.

In conclusion, this research addresses, for the first time, the implementation of vaccine clinical trials in Latin America countries and the contribution of the local researcher to the project, especially with their knowledge about the communities intervened. But it also highlighted some of the aspects that affect the implementation of clinical trials, such as the labour conditions in academia, which induce turnover, and the lack of harmonisation among clinical trial regulation in the region. In conclusion, the model proposed allowed me to address simply the complexities that take place in the production of knowledge products in multi-organisational clinical trials in Latin America countries.

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# Abbreviations

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<b>ANVISA:</b>	The Brazilian Health Regulatory Agency
<b>CMV:</b>	Cytomegalovirus Disease
<b>COFEPRIS:</b>	The Federal Commission for the Protection against Sanitary Risk - Mexico
<b>CRF:</b>	Case Report Form
<b>CRO:</b>	Contracted Research Organisation
<b>DNDi:</b>	Drugs for Neglected Diseases
<b>DKW:</b>	Distributed Knowledge Work
<b>DVI:</b>	Dengue Vaccine Initiative
<b>eCRP:</b>	Electronic Case Report Form
<b>EMA:</b>	European Medicines Agency
<b>FDA:</b>	Food and Drug Administration of the USA
<b>GCP:</b>	Good Clinical Practices
<b>GCP-ICH:</b>	Good Clinical Practices - International Conference of Harmonization
<b>GP:</b>	General Practitioner
<b>HIV:</b>	Human Immunodeficiency Virus
<b>ICF:</b>	Informed Consent Form
<b>ID:</b>	Intradermal
<b>IMSS:</b>	Mexican Institute of Social Welfare
<b>IND:</b>	Investigational New Drug
<b>INVIMA:</b>	Colombia's National Food and Drug Surveillance Institute
<b>IRB:</b>	Institutional Review Board
<b>KIP:</b>	Knowledge Intensive Project

<b>KPO:</b>	Knowledge Processes Outsourcing
<b>MRC:</b>	Medical Research Council
<b>NIH:</b>	National Institutes of Health
<b>PAHO:</b>	Pan American Health Organisation
<b>PRNT:</b>	Plaque Reduction Neutralisation Testing
<b>R&amp;D:</b>	Research and Development
<b>SC:</b>	Subcutaneous
<b>SMO:</b>	Site Management Organisations
<b>SOPs:</b>	Standard Operating Procedures
<b>The USA:</b>	The United States of America
<b>USP:</b>	The University of Sao Paulo
<b>WHO:</b>	World Health Organisation

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# Chapter 1: Introductory chapter

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## 1.1. Introduction

The success of a multi-organisational knowledge-intensive project lies in the use of knowledge in action and its flow across organisations. The main objective of this thesis is to develop and evaluate a conceptual model to study two elements in the management of knowledge in multi-organisational projects. The first element is the study of the flow of knowledge across organisations working on multi-site clinical trials, and the second element is the study of the use of knowledge by people in the organisations to meet their productive enquiries related with the project. To achieve the objectives, the principal research question of this thesis is: ***How does knowledge flow across organisations and is employed by people in their firms to implement the clinical trial and obtain their respective results?***

To answer this research question, a conceptual model was proposed and evaluated through a multi-case study design of three multi-organisational clinical trials taking place in Colombia, Brazil and Argentina. The purpose of this introductory chapter is to present to the reader the context in which this thesis takes place; that is, the implementation of sponsored clinical trials in Latin America and its evolution through time.

The first section of this chapter seeks to provide the context of this research and discusses the changes in the landscape of the clinical trials over the last 20 years. This discussion defines the clinical trials as multi-organisational projects, where each organisation has specific and clearly defined responsibilities in the context of the whole trial. This review gives place to the research questions addressed in this thesis.

In the second section of this chapter, I provide an overview of the structure of this thesis that leads to the answer of this principal research question and the content of each one of the chapters. As a result of this chapter, I expect that the reader has an understanding of the basics of this project, its contributions and an overview of the thesis.

## 1.2. Clinical trials like multi-organisational projects

A clinical trial is a medical experiment that has the main aim of elucidating how a new drug or biological product is going to behave in the human body and in a population. The implementation of a clinical trial has shifted over the course of history since the first formal clinical trial about scurvy on sailors was described by Lind (1753). At that time, clinical research was conducted by physicians individually, who planned and executed trials with their patients, and they wrote their results in diaries or reports. Nowadays, clinical trials to evaluate new compounds are multinational, coordinated mainly by pharmaceutical companies that have the economic means to sponsor the high cost associated with clinical research.

The scientific basis of the modern clinical trials was created in the nineteenth and twentieth centuries. In the nineteenth century, researchers widely employed statistics and the “calculation of probabilities” and mathematical concepts in the design of clinical trials (Matthews 2006). The designing of protocols, the randomisation of participants, and the double blinding of the trials are elements introduced in the design of the clinical trials in the nineteenth century (Stolberg 2006). The knowledge created in these studies paved the way for the first randomised controlled trial carried out in 1946 by the MRC in the United Kingdom to evaluate the use of streptomycin in pulmonary tuberculosis. This trial is a model to conduct clinical research because of its meticulousness in the design and implementation.

The lack of harmonisation of requirements to implement trials and accept the results across countries pushed the harmonisation of procedures to conduct clinical research. The declaration of Helsinki, the Nuremberg code (Pocock 1980) and the Belmont Report, and the need to harmonise procedures among the USA, Japan and Europe were the foundations for the creation of the Good Clinical Practices (GCP). The GCP is “an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects”(ICH Harmonised Tripartite Guideline 1996, 1). As the century evolved, the pharmaceutical industry increased the implementation of multi-national clinical trials in emerging regions of Eastern Europe, Latin America, Asia, the Middle East and Africa (Jeong et al. 2017), where recruitment is faster and with a lower cost. With the globalisation of

clinical research, the GCP-ICH have been adopted by other countries around the world to approve the implementation of clinical trials in their territories. In this way, in the last century, all the knowledge and regulatory frameworks defined the bases for the execution of international clinical trials in this century.

Over the second half of the twentieth century, the pharmaceutical industry led the implementation of clinical trials to evaluate new molecules where the participation of academic institutions decreased, taking a secondary role (Chopra 2003). Clinical trials account for approximately 42% of the research and development funding spent by the pharmaceutical industry in the development of new products (Thakur and Contractor 2008). The time between pre-clinical and clinical phase to obtain a product licence ranges from 6.8 to 18 years (Cockburn 2007). Over the last 30 years, there has been a shift in the industry to speed up this time. Pharmaceutical companies are outsourcing traditional in-house activities to foreign affiliates and Contracted Research Organisations (CROs) (Azoulay 2004; Thakur and Contractor 2008; Jeong et al. 2017). These CROs provide outsourced services to the pharmaceutical, biotechnology and medical device industries, including drug discovery, preclinical research, clinical research, protocol design, pharmacovigilance, regulatory services, clinical trial management, commercialisation, data management analysis and reporting (Delancey Street Partners LLC 2016; Ukwu et al. 2011b).

There are four primary drivers required to outsource the clinical trial project to foreign countries. Firstly, there is the need to include diverse ethnic backgrounds when studying drug performance (Yasuda, Zhang, and Huang 2008). Secondly, trials are becoming more multinational because there is a need to identify the influence of intrinsic (environmental differences, culture diet, medical treatment) and extrinsic factors (genetic, people's weight, physiological differences) on the variations in the drug response (Bairu, Spector, and Chin 2013; Aban et al. 2008). Thirdly, there is a need to decrease cost; it has been reported that the outsourcing of clinical trials to Asia or Latin America represents savings of around 50% and 90% (Bairu, Spector, and Chin 2013). Fourthly, the evaluation of biological products or medicines to treat or prevent endemic diseases must be conducted in the endemic areas, so trials are outsourced to CROs that have experience working in these locations. Some of these reasons to outsource clinical trials are shared with other industries that also outsource services,

like the motivation to reduce cost or because the location provides an advantage to introduce a product or service (Anderson Jr. and Parker 2013).

The outsourcing of clinical trial projects has taken place since the mid-80s in the USA. However, in Latin America, the rate of this activity has increased only over the last 20 years, and the operations outsourced are mainly the execution of the clinical trial and monitoring activities. For some scholars, this change has represented a risk in the loss of knowledge by the pharmaceutical firms putting in risk innovation (Lowman et al. 2012). Therefore, the internationalisation of clinical research, plus the outsourcing of activities, have transformed the implementation of clinical research and made a clinical trial a multi-organisational project (Ukwu et al. 2011a) involving multiple organisations, in some cases in various locations. Then, a research activity that was originally conducted and led by individual researchers is now a multi-organisational activity, highly regulated and structured, with defined guidelines and procedures. Then, the study of clinical trial projects can contribute to understanding key issues in another outsourced project, which will be discussed below.

### 1.2.1. Clinical research in Latin America and research questions

In the last 12 years, the participation of Latin America in the business of clinical trials has significantly increased. The number of registered trials in the region augmented on average 22% between 2002 to 2006 (Thiers, Sinskey, and Berndt 2008). In the specific case of vaccines registered in the database ClinicalTrials.gov, of the 7,244 clinical trials to evaluate vaccines, 421 trials contain data from Latin America (Mexico, Central America and South America). This number is higher than the number of trials conducted to evaluate vaccines in Africa, India, Southeast Asia, and Middle Eastern countries (Clinicaltrials.gov 2017). This fact shows the relevance of the region in the clinical trial market to evaluate vaccines.

In the context of clinical trials sponsored by the pharmaceutical industry in Latin America, the sponsor used to outsource the project execution directly to the principal researchers. In these trials, the sponsor, through their local branches, directly transferred the protocol to multiple research sites and trained them directly; providing all the relevant information to execute the project. Therefore, obtaining clinical evidence was the product of the coordinated work between two types of organisations,

the sponsor and the research sites, where the outcome of one team was the input to the other; creating a bidirectional knowledge and data flow. However, over the last 20 years, the clinical trial industry has been revolutionised by the presence of a third actor – the Contract Research Organisation (CRO) (Arnum 2014; Getz 1997; Ukwu et al. 2011a). CROs have significantly transformed how clinical trials are conducted not only in Latin America (Petryna 2006) but also throughout the world. In the context of Latin America, the presence of CROs, especially in the field of clinical trials, has completely changed the ‘two organisations’ and bi-directional relationship separating the interaction between the sites and the sponsor, where the CRO becomes the sponsor’s intermediary in the country (Smed and Getz 2013).

More recently, organisations like SMOs (Site Management Organisations) have emerged as a kind of umbrella organisation to coordinate the research sites and the implementation of the protocol in multiple settings, mediating the relationship between sites, principal researchers and the CROs. These SMOs emerged in the USA around twenty years ago (Maloff 1999), and ten years ago, private SMOs appeared in Latin America, especially in Brazil and Colombia. Additionally, to overcome the lack of local research capabilities, temporary SMOs have also been configured to coordinate inexperienced research sites and train them, as some of the cases studied in this project indicate. In this sense, SMOs have become a relevant actor in the transfer of information and management of the trial. Therefore, the participation of multiple actors involved in the clinical trials makes the implementation of the project fragmented, where each firm contributes with their knowledge and skills.

In a clinical trial, knowledge is the primary productive factor, and organisations participating in the project constantly exchange it. The management of knowledge, which is core in a trial, is usually left over by people researching the clinical trial, or scholars reduce it to the study of the management of documents like archives and emails. I consider that holding knowledge or having it in documents and protocol is not enough to be successful in the project. I recognise that what matters in the study of knowledge in a clinical trial is the understanding of the use of knowledge to execute the tasks, and how knowledge flows and is transformed into products over the project. Then, in this new multi-organisational context, where multiple types of actors are part of the implementation of a clinical trial, emerges the next question:

**How does knowledge flow across organisations and is employed by people in their firms to implement the clinical trials and obtain their respective results?**

To answer this principal research question, it is necessary to identify the actors involved in the production of the clinical evidence and their results. In this research, the two principal organisations that will be studied to understand the flow of knowledge, data and information *are the sponsors and the research sites*. In this thesis, I consider the CRO and the SMOs as intermediary organisations, and their study is associated to this intermediary role because they do not produce the critical knowledge products that give place to the collection of the clinical evidence. Based on this distinction, in Chapter 2, I address the origin of these three sub-questions and the three central sub-research questions in this thesis are:

**Sub-Q1: How did the sponsor acquire and use knowledge, data and information to design the clinical protocol?**

**Sub-Q2: To what extent does the structure designed by the sponsor to transfer knowledge, the permeability of the research sites, and the previous experience of people working on the project influence the acquisition of knowledge in the research sites?**

**Sub-Q3: How is knowledge employed in the clinical research sites to produce the clinical data and transfer it to the sponsor?**

The answers to these three sub-research questions provide the basis to understand how knowledge flows across organisations in the multi-organisational project and how knowledge is employed in two main activities of the project: the creation of the protocol and the obtaining of the clinical data. The answer to this question is not only relevant to understand a new dynamic in the implementation of clinical trials. The answer can help clinical researchers to learn from other researchers' experience to implement clinical trials. To answer these research questions, I will use concepts from knowledge management literature, primarily from the literature of knowledge management of outsourcing projects and the literature of knowledge 'models, work and processes', as will be detailed below.

## 1.3. Chapters overview

With the aim of addressing the objectives raised above and answering the research questions, this thesis has a theoretical chapter, a methodological chapter, four main chapters, and a conclusion chapter. Below, I present a summary of the content of each chapter.

### 1.3.1. Chapter 2: Theoretical frameworks

In this chapter, I present the sub-research questions and I address extensively the origin of these questions based on the gap present in the literature of clinical trials and previous research on knowledge management associated with clinical trials. The second section of this chapter addresses the definition of knowledge in the field of organisational studies and justifies the adoption of the knowledge definition proposed by Cook and Brown (1999). The third section of this chapter introduces the concept of Knowledge-Intensive Projects (KIP) and defines clinical trials as KIP. The fourth section presents previous research on the management of knowledge in multi-organisational activities and projects such as KIP and outsourced activities. In the fifth section, I propose a model to answer the research questions and study *the flow of knowledge across organisations and its use to produce the productive enquiries*. The model offered to explain the management of knowledge within or across organisations combines models and factors from different areas of studies. The model has its roots in the literature of knowledge ‘models, work and processes’ (K. Grant 2011, 121) and I complement it with the concept of interdependency proposed by Thompson (1967) and the concept of permeability that I develop. Also, two key factors are identified in the literature of project outsourcing: people’s previous knowledge and the structural dimension to transfer knowledge (sources, channels and network structure) were added to the model. The last section presents a summary of the chapter.

### 1.3.2. Chapter 3: Methodological chapter

In this third chapter, I present the research design, data collection and data analysis. In the first section, I introduce the research design of this project, where I discuss the process of selecting a qualitative multi-case study approach and the advantage of this design compared to others to achieve external and internal validity on the study. In this

section, I explain the systematic literature review implemented to select the three dengue vaccine cases and the countries (Colombia, Brazil and Mexico) included in this research. In the second section, I explain the use of interviews to collect data, the process of accessing to information sources, the experience implementing the fieldwork and the limitation raised over the data collection. In the third section, I introduce the procedure for analysing the collected data using a grounded theory 'Framework' approach (Jane and Liz 2011). This method allowed comparisons and associations between and within cases, being entirely suitable for the research design of this project, permitting a systematic treatment of all units of analysis. In the fourth section, I present the ethical consideration of this research, and in the fifth section, I provide a reflection on my experience doing this research. The last part gives a summary of the chapter.

### 1.3.3. Chapter 4: Use of internal and external knowledge by the sponsor to design the clinical trial

This chapter answers the first sub-research question of this thesis: ***How did the sponsor acquire and use knowledge, data and information to design the clinical protocol?*** The conceptual model proposed in the theoretical chapter was employed to answer this question. In this sense, I analyse two aspects associated with the use of knowledge to design the protocol. The first one is how research teams internally manage their knowledge and previous results to create the clinical trial. Secondly, I analyse the acquisition of knowledge from external sources, considering the sources and channels employed to acquire data and information and the permeability of people towards external knowledge and information. The chapter is divided into four sections. The first one is the introduction. The second section addresses the management of knowledge and information residing within the boundaries of the sponsor's clinical team to design the protocol. This section is divided into four sub-sections, each one dedicated to the use of different types of knowledge and information. 1) The use of guidelines to design the protocol. 2) The use of previous clinical and pre-clinical results. 3) The use of knowledge to create the protocol. 4) The influence of the commercial interest of the sponsor designing the protocol. The third section discusses the acquisition of external knowledge, information and data to design the protocol. This section is divided into two sub-sections. The first sub-section addresses the acquisition of demanded information and the structures employed; the second sub-section



discusses the permeability of the clinical teams to external knowledge and information not requested. The fourth section is the conclusion of this chapter.

#### 1.3.4. Chapter 5: Acquisition of knowledge and information by the research sites

This chapter aims to answer the second research question of this thesis: *To what extent does knowledge-base of people working on the project, the structure designed by the sponsor to transfer knowledge, and the permeability of the research sites influence the transfer/acquisition of knowledge in the research sites?* To answer this question, I will discuss the interdependency between the sponsor and the research site, and how these three factors positively or negatively impacted the transfer/acquisition of knowledge and information between the organisations. This chapter is divided into four sections. The first section is the introduction. The second section discusses the influence of the structure defined by the sponsor on the transfer of information and its respective acquisition by the research sites. This section is divided into three sub-sections. The first sub-section discusses the benefits of direct communication between the sponsor and the research sites. The second and third sub-sections are focused respectively on the influence of intermediary actors such as the CROs and the SMOs on the transfer and acquisition of knowledge and the permeability of the teams towards these intermediaries. The third section discusses the relevance of the previous experience of the research sites on the acquisition of knowledge. This section is divided into three sub-sections. The first sub-section explains the configuration of the clinical teams and its relevance to the knowledge acquisition. The second sub-section focuses on the acquisition of knowledge of experienced research sites, and the third sub-section discusses the acquisition of knowledge of new research sites. The last section of this chapter provides the conclusions.

#### 1.3.5. Chapter 6: Opening the black box of the research sites. Implementation of the protocol

This empirical chapter answers the third research question of this thesis, which is: *How is knowledge employed in the clinical research sites to solve the productive enquiries related to the production of clinical data and its transfer to the sponsor?* In this chapter, continuing with the use of the model proposed, I discuss at

the intra-organisational level how the personnel at the research sites use the acquired knowledge from the sponsor and the knowledge that they already had to implement the project, produce the data and transfer it to the sponsor. Answering this question, I pay particular attention to the know-how that is employed in the activities and the contextual knowledge used by the staff to advance on the project. This chapter separately addresses the key productive enquiries associated with the production of clinical data in five sections. The first section is the introduction. The second section discusses the integration and use of knowledge in the research sites. I discuss separately the standardisation of procedures and the use of knowledge in practice. The third section discusses learning loops that take place over the trial. The fourth section focuses on the transfer of data and the storage of knowledge, where I discuss the barriers to storing knowledge in the organisations once the project concludes. The fifth section presents the chapter's conclusions.

### 1.3.6. Chapter 7: Discussion and conclusions.

This chapter aims to bring together the evidence collected and presented through the empirical chapters, the model proposed in this research and the literature previously discussed. In this way, in this chapter, I expect to provide a solution to the central research question of this thesis, identifying how knowledge, information and data are transferred, acquired and employed within and across organisations over the course of a multi-organisational project. This last chapter is divided into two main sections. The first section discusses the main empirical findings associated with each main research question. This section has three sub-sections, one for each research question. The second section explains the theory addressing each one of the steps of the model proposed. This section is divided into four sub-sections. The first sub-section discusses the knowledge transfer and the role of intermediaries. The second sub-section discusses the acquisition of knowledge and the influence of the previous experience and the permeability on this process. The third sub-section focuses on the use of knowledge in the productive enquiries. The fourth sub-section introduces a reviewed model complemented based on the evidence obtained in this thesis and discusses the further areas of research.

In summary, this thesis makes several theoretical and empirical contributions to the current literature in the emerging field of knowledge management in outsourced projects. To the best of my knowledge, this research is the first one that addresses at the same time the study of knowledge management at the inter-organisational and intra-organisational level in multi-organisational projects, presenting a holistic view of the process, including the transformation of knowledge and people's contributions. This study addresses the knowledge flow from the beginning of the project until later stages. Second, this study makes a significant contribution to the mentioned field by proposing and evaluating a conceptual model to study the knowledge flow and its use in multi-organisational projects employing models from the knowledge management literature to study intra-organisational dynamics.

This research proposes a robust model, that integrates critical steps and critical factors that influence the flow of knowledge in the multi-organisational project. As a next step, this model can be employed to study other industries to be validated before it can be generalised to the universe of multi-organisational knowledge-intensive projects. Nonetheless, this work advances on the study of multi-organisational projects and provides the evidence to suggest that this model explains the flow of knowledge in the context of clinical trials managed by different kinds of firms like pharmaceutical companies, biotech companies, or public research organisations. Third, this thesis introduces the concept of permeability, which is defined, enriched and evaluated through the empirical data collected. In this way, the theoretical framework proposed in this project sheds light on how knowledge is managed at the inter and intra-organisational level by the actors participating in outsourced knowledge-based projects.

## 1.4. Summary

In this introductory chapter, I have presented the context of this research and an overview of the content of the following chapters. In the first section, I introduced the evolution of clinical trials over the last two centuries, briefly regarding the actors that participate in the trials, the scientific bases developed in the UK to implement clinical research and the internationalisation of clinical research. I consider this section essential because it allows an understanding that the actual process of implementing

clinical research is the result of a dynamic process, which can also change in the future. Then, this research is a picture of a specific moment in the evolution of clinical research. Based on this panorama, I introduced the principal research question and outlined the sub-research questions. In the second section of this thesis, I presented an outline of this thesis and the contents of each one of the following chapters.

# Chapter 2: Research questions and theoretical framework

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## 2.1. Introduction

This chapter aims to introduce the research questions of this project and provide the theoretical and conceptual framework to answer these questions. In this first section, I elucidate the research gaps in the study of the management of knowledge in the context of clinical trials, specifically in Latin America. These gaps are the basis to propose the principal research question and sub-research questions of this research. The second section of this chapter presents the definition of knowledge in this thesis. In the third section, I define a clinical trial as a knowledge-intensive project (KIP). In the fourth section, I introduce the previous research on the management of knowledge in KIP and outsourced projects and the different fields that have contributed to this study. In the fifth section, I propose a model to explain the flow and use of knowledge, data and information across organisations. In this model, I consider the critical steps raised in the literature of knowledge ‘models, work and processes’ (K. Grant 2011, 121) and key factors identified in the literature of knowledge management in outsourced projects. At the end of this section, I present how I’m going to use this model to answer each one of the sub-research questions stated in this thesis.

## 2.2. Knowledge gap and research questions

Regarding the outsourcing of clinical trials in Latin America or other regions, some clinical researchers have discussed within the clinical community the lessons learned by researchers implementing clinical trials and their reflections and suggestions to improve clinical research in these regions. Some aspects covered by these scholars in the clinical trial field are:

1. Challenges in implementing public-private collaborations to evaluate vaccines (Eskola and Kilpi 2011).

2. How the regulation in countries different to the USA and western Europe regulations influences the trial implementation (Aban et al. 2008; McNay et al. 2002; Duley et al. 2008; Choi and Ko 2010; Bairu, Spector, and Chin 2013).
3. The need to create research capabilities in rural areas to implement trials (Ukwu et al. 2011a).
4. The challenges and benefits of implementing trials in these countries (Chin 2012; Aban et al. 2008; Bairu, Spector, and Chin 2013).
5. The cost efficiencies related to the access to patients, the presence of competent and enthusiastic researchers who can implement complicated studies ("The Top Reasons for Conducting a Clinical Trial in Latin America" 2014; Chin 2012; Ukwu et al. 2011a).
6. How to improve data quality (U.S. Department of Health and Human Services Food and Drug Administration 2006; Friedman et al. 2015; Chan et al. 2013; Gassman et al. 1995; Knatterud et al. 1998; Meinert 2012).

But the actual using of knowledge over the course of these projects has been less study, which is really surprising because, as I said before, in these projects people's knowledge is the principal production factor and main product.

In the context of clinical trials, scholars in the field of management and innovation have studied some aspects associated with the management of knowledge over the course of the project. These researches have focused on where there is a risk of the pharma company losing knowledge and control over the project (Lowman et al. 2012; Aban et al. 2008; Thakur and Contractor 2008); the way in which decisions are made to determine what activities to outsource (Azoulay 2004); the impact of the clinical trial on the knowledge of the contractor (Thakur and Contractor 2008); the transfer of lessons learned from the research sites to the sponsor (Smed and Getz 2013); the ethical aspects of the outsourcing (Fisher 2008; Kamat 2014) and the adverse effect that the CROs have over this transfer process (Smed and Getz 2013).

Regarding knowledge production in outsourced clinical trials, Azoulay (2004) has been the first one to address this issue. His study took place when the pharmaceutical industry was shifting from using internal monitors to outsource this activity to CROs.

He discussed the role of monitors in the production of data and knowledge within the clinical trial. In his view, outsourced monitors (CROs) were oriented to produce data about the quality of data obtained by site researchers, whereas industry monitors (working for the pharma company) focused their work on identifying causal associations and developed new knowledge useful for the project. Nonetheless, besides this study, the participation of each one of the actors in the clinical trials, about how knowledge flow and how different organisations contribute with their knowledge, has been little researched, and much less in research sites located in Latin America. This understanding is especially relevant in the clinical trial industry, as what is prevalent in the industry is a combination of offshoring to foreign affiliates as well as outsourcing to domestic and international CROs and SMOs, and knowledge has to flow through these vendors.

Mistakes, omissions or misunderstandings on the transmission of information can have a direct influence on the project's execution, leading to errors in the data, the production of wrong information and, at the end, the obtaining of inaccurate evidence. All this can have critical consequences for people's health if clinical trials' results are incomplete and the product is introduced into the market (as one of the cases will illustrate, Chapter 4. Pg. 84). To my knowledge, besides Azoulay's (2004) study there has not been any research published that analyses the flow of knowledge, information and data and its use across the different actors that are part of the clinical trial. In a world that is more globalised and where projects are outsourced and fragmented among different firms, there is a need to understand, in the context of multi-organisational projects, the flow of knowledge across organisations and its actual use in the specific project, and not only how firms individually become more competitive as a result of a project. For this reason, the principal objective of this study is to investigate the flow of knowledge and its use across the actors that participate directly in the project, from its design to its implementation. In this sense, the principal research question that this project aims to answer is:

**How does knowledge flow across organisations and is employed by people in their firms to implement the clinical trials and obtain their respective results?**

This research provides new evidence on how knowledge is transformed, created, implemented in practice, and multiplied in a fragmented landscape composed of the multiple actors that participate in the design and execution of clinical trials. This research question is relevant because, each day, more research projects in different fields are implemented in collaboration among various groups, where knowledge flows and knowledge products are interdependent.

This panorama is not only present in medical fields; in different industries, the outsourcing of key activities has been the constant of this century, especially in the IT sector, where the influence of outsourcing activities over the project results have been actively debated (Tafti and Zarb 2006). Therefore, I consider that the present research can contribute considerably to the study of knowledge in multi-organisational projects and give light to the aspect to be considered in the planning and execution of these projects. Of course, each project and industry has its particularities. Nonetheless, lessons learned in each industry can be shared, so in this way, this project can be relevant for multi-organisational projects in other fields.

### 2.2.1. Sub-research questions

The answer to this research question demands to know what the main activities in a clinical trial are, and the actors responsible for these. In this way, it is possible to analyse the flow of knowledge among organisations and their products. The first activity in a clinical trial is *the design of the research protocol*. The sponsor is responsible for creating the protocol, and the national regulatory agency of each country has to approve it. The second activity is the transfer of the protocol to the research sites to obtain the clinical data and other documentation associated with the project. In this way, the third critical activity is the implementation of the project by the sites. Finally, the fourth activity is the transfer of clinical data to the sponsor and its analysis to obtain the clinical evidence about the medical product under evaluation. Therefore, in total we have four main activities associated with the use and transfer of knowledge and three concrete knowledge-products are created and transferred. Firstly, the protocol designed by the sponsor; secondly, the clinical data produced exclusively by the research sites, and finally, the project result obtained only by the sponsor. This chain will be the one



addressed over the course of this thesis studying the use of knowledge and the demand or transfer of required knowledge, data and information to achieve the goals.

The sponsor is the organisation responsible for the clinical trial. The sponsor's first responsibility is to design the project's research protocol. The protocol is a formal document that describes the objectives and all the processes and activities to be undertaken systematically and accurately in every single clinical site through the trial (Chin 2012; Knatterud et al. 1998). The information in the protocol consists of the objective(s), the endpoint, the methodology, statistical considerations, the logistics of the study, product dosage, patients' inclusion and exclusion criteria, randomisation procedures, among others (Chin 2012; Knatterud et al. 1998; ICH Harmonised Tripartite Guideline 1996). Scholars have extensively discussed the need for a multidisciplinary perspective to design the protocol (Chin 2012) and the need to address the design aspects, such as scientific and logistic issues, data management, implementation and data analysis (Ottevanger et al. 2003; Goodarzynejad and Babamahmoodi 2015; Pocock 1980). Nonetheless, the study about the acquisition and use of previous knowledge to design the clinical protocol has been less explored in the literature. I consider it fundamental to understand, from the sponsor's perspective, how the clinical protocol is created to better understand the flow of knowledge across organisations in a clinical trial. Therefore, the first sub-research question of this thesis is: ***How did the sponsor acquire and use knowledge, data and information to design the clinical protocol?*** Chapter 4 provides the answer to this question, where I discuss how information flows towards the sponsor to create the protocol and design the clinical trial.

Once the sponsor creates the protocol, the next stage is to transfer this document to the organisations responsible for the project's execution. Within the clinical trial community, researchers have discussed that data's validity may be dependent on the level of training received by the personnel working in the clinical trial and their familiarity with the study protocol (Gassman et al. 1995). According to the literature, the sponsor provides training to the sites. This training has the purpose of ensuring that all proceedings follow the practices in the industry, especially the GCP and the project documentation (Ukwu et al. 2011a). Research conducted by Subramaniam and Dugar (2012) emphasises the value of knowledge transfer and mentoring. Training does not only take place at the beginning of the trial. The identification of variation in the

clinical data demands additional training or modification of procedures to solve these issues and minimise the probability of future occurrences of deviations (Knatterud et al. 1998; Minisman et al. 2012; Ukwu et al. 2011a). For this reason, studying the training and transfer of knowledge becomes relevant to analyse the flow of knowledge.

The literature of knowledge management in outsourcing projects has discussed the transfer of knowledge from contractors to providers. Bustinza et al. (2010) argue that to create a shared knowledge, the transfer of knowledge from contractors to suppliers becomes a subject of high relevance in multi-organisational projects. In this way, people can be on the same wavelength to understand the personnel in the other organisation and they can also learn the required information to execute a task. In this literature, three key factors can be identified for influencing the transfer of knowledge and information in an outsourced project. The first one, the structure created by the sender to transfer knowledge, data and information to the receiver. The second one, the previous experience and knowledge that the receptors have. And the third one, the openness of the people to accept and use the knowledge received (below I discuss these three elements), which I call permeability in this thesis. In a changing context, with the presence of new actors like the CROs and SMOs, little has been researched about the influence of these intermediaries on the acquisition of knowledge or the influence of the hierarchy to transfer knowledge on the acquisition of knowledge by the research sites. And much less attention is paid to the permeability<sup>1</sup> of these last ones towards external knowledge.

Therefore, the second research question that emerges in this thesis is: **To what extent does the structure designed by the sponsor to transfer knowledge, the permeability of the research sites, and the previous experience of people working on the project influence the acquisition of knowledge in the research sites?** This question is addressed in Chapter 5, where I discuss the impact of these factors on the transfer of knowledge and its acquisition by the research sites.

The implementation of the protocol by researchers and staff in the research sites is an aspect that has received less attention, despite its relevance to the project. Research

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<sup>1</sup> Concept developed in the theoretical framework that has its roots in the not-invented here syndrome.

sites produce the clinical evidence and transfer the results to the sponsor, who analyses the data. Scholars have argued that the staff behaviour over the clinical research can compromise the safety and integrity of the trial and the subjects (Ottevanger et al. 2003; van Dongen 2001; Ippoliti 2013; Barnes and Florencio 2002b; Barnes and Florencio 2002a). In turn, this behaviour influences the procedures to recruit participants (Geldenhuis et al. 2012; Goodarzynejad and Babamahmoodi 2015). Some of the problems described regarding the trial implementation include protocol violations, consent violations, fabrication of data, falsification of data and financial conflict of interest (Habermann et al. 2010; Gardner, Lidz, and Hartwig 2005; George 2016). To address these issues, many papers have focused on discussing how to improve data quality in clinical trials in general (U.S. Department of Health and Human Services Food and Drug Administration 2006; Friedman et al. 2015; Chan et al. 2013; Gassman et al. 1995; Knatterud et al. 1998; Meinert 2012). The majority of these papers advocate for the implementation of cost-effective procedures that guarantee the validity of the primary results (Knatterud et al. 1998), where some strategies to keep data quality include auditing, planning, analysis, inspection and tests of techniques (Ottevanger et al. 2003).

However, scholars have limited their study about research sites' dynamics to the problems associated with data quality, arguing that personnel at the sites do not contribute with their knowledge to the project (Fisher 2008). Far too little attention has been paid to the contribution of the sites to the project and the use of knowledge by physicians and other site's members to obtain the clinical evidence. Therefore, the research question that emerges regarding the implementation of the project and the transfer of data is: ***How is knowledge employed in the clinical research sites to solve the productive enquiries related to the production of clinical data and its transfer to the sponsor?*** Chapter 6 provides an answer to this research question, where I open the black box of the contributions of the research sites.

Then, answering the three research questions stated above, I expect to solve the central research question of this thesis, providing light on the flow of knowledge across organisations participating in multi-organisational projects and the use of knowledge in the main activities associated with a clinical trial in Latin America Countries.

## 2.3. Knowledge definition

Until this point, I have introduced the research question, and I have focused the discussion on the literature related to clinical trials. Nonetheless, I have not defined knowledge, which is fundamental to set the epistemological basis of this thesis.

Defining knowledge is not a simple task because, in the field of knowledge management, where this thesis is placed, multiple perspectives and definitions of knowledge have emerged. For example, in some cases knowledge is seen as a condition to access information (McQueen 1998), other researchers see knowledge as an asset or a production factor to make the firm more competitive (Bollinger and Smith 2001; Bustinza, Molina, and Gutierrez-Gutierrez 2010; Samoilenko and Nahar 2011; Maier 2004), other researchers define knowledge as an outcome of organisational learning (Alavi and Leidner 2001; Bukowitz and Williams 1999; M. H. Meyer and Zack 1996). Then, in organisational studies and knowledge management, a consensus about knowledge classifications does not exist, making it challenging to define knowledge. Philosophers and sociologists of science have addressed the question of knowledge for a long time, but an agreement has not been reached.

Despite this situation, the management of knowledge has become a fundamental aspect studied in organisations (Kogut and Zander 1992; Nonaka and Takeuchi 1995; Tsoukas and Mylonopoulos 2004; Evans, Dalkir, and Bidian 2014), where two different perspectives (definitions) about knowledge prevail. Tsoukas (1996) named the first perspective as a taxonomic view of knowledge, where scholars classify knowledge according to its content. Based on these classifications, scholars recommend strategies, routines and techniques to generate, encode, share and transfer the different types of knowledge in the organisation (Richard Rex Nelson; Sidney G. Winter 1982; Nonaka 1994; Newman and Conrad 1999; Maier 2004). This taxonomy perspective is rooted in the taxonomy proposed by Polanyi (1966), of tacit and explicit knowledge, which has been the base to introduce multiple knowledge dichotomies such as:

1. General vs specific (Samoilenko and Nahar 2011)
2. Local vs universal (Oluikpe, Sohail, and Odhiambo 2011)
3. Codified vs uncoded (Oluikpe, Sohail, and Odhiambo 2011)

4. Procedural vs declarative (Wiig 1993)
5. Individual or social knowledge (Spender 1996).

Nevertheless, authors such as Tsoukas (1996) have criticised this dichotomic or discretionary view about knowledge. For him, this division does not recognise that tacit and explicit knowledge are inseparable and knowledge cannot always be classified in categories without considering the interlinks among them. Also, tacit knowledge is a necessary component of all knowledge (Tsoukas 1996).

The second view about knowledge, in an organisation, aims to articulate know-how and know-what. Know-how is the ability of people to put into action what is known (Seely Brown and Duguid 1998), and the know-what represents an understanding of the generative process that constitutes phenomena (Garud 1997). This vision of knowledge is rooted in the separation between learning and use. Under this vision, there has been a concern about how to join the study of these two activities to understand how, in an organisation, learned knowledge is employed, and how the learning context influences the use of knowledge in action (Brown, Collins, and Duguid 1989). In this second view of knowledge, knowing what to do, by itself, does not enable the execution of the task, so developing the know-how in action is fundamental to implement any work.

In this second view of knowledge, Cook and Brown (1999) suggested that within organisations there exist two epistemologies of knowledge: the 'epistemology of possession' and the 'epistemology of practice'. The epistemology of possession sees knowledge as 'something' that people have in their heads, and they can acquire and transfer. The epistemology of practice is about the use in the execution of the task of what is known; this means "knowing as part of the action". According to Cook and Brown (1999), these two epistemologies are complementary and co-exist, and they are NOT oppositional. People possess knowledge, and it is through action that they identify if this content and procedures are enough to implement the task. If knowledge possessed is not sufficient or adequate to know how to execute a task (epistemology of practice), new knowledge, know-what, and know-how has to be acquired (epistemology of possession) until the individual is capable of culminating the task. For these authors, possessed knowledge must be seen as a "tool at the service of knowing,

not as something that, once possessed, is all that is needed to enable action or practice” (Cook and Brown 1999). Under this perspective, individuals develop new knowledge in practice, and this new knowledge becomes a new know-what and know-how for future activities and can help to solve the new problems. For Cook and Brown (1999), the knowledge possessed by people only makes sense once people implement it in practice, in productive inquiries.<sup>2</sup> In this way, the epistemology of possession and practice are interlinked continuously.

It is important to clarify in this thesis that the ‘epistemology of practice’ is not the same as practice theory or communities of practice, which can be easily confused by the reader and can lead to misinterpretations of the rest of the document. Practice theory is a broad intellectual landscape that has “emphasis on explaining the emergent constitution of the socio-material world through the micro-dynamics of everyday life in organisations” (Feldman and Orlikowski 2001, 1250). Practice theory argues that “everyday actions are consequential in producing the structural contours of social life” (Feldman and Orlikowski 2001, 1241). In other words, practices produce an organisational reality, which is dynamic and accomplished in ongoing everyday actions. On the other hand, a community of practice is the building block of a social learning system. In these communities, people learn, display capabilities and are evaluated by peers, who determine if they are trusted as a partner of the community (Wenger 2000). In contrast, the epistemology of practice is oriented to see how what people know (possessed knowledge) is used in everyday life rather than understanding the origin of routines or explaining an organisational reality or how people learn within their communities. Of course, this does not mean that one study cannot address at the same time the study of the epistemology of practices and possession, and the study of a community or the emergence of routines in an organisation, but this is not the scope of this research.

The focus of this thesis is to understand the flow of knowledge across organisations and its use to produce the knowledge products in each one of the organisations. This objective implies that this research considers knowledge as an object transferred,

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<sup>2</sup> A productive inquiry is a form of knowing that seeks an answer, solution or resolution to questions or problems, ranging from fixing a photocopier to the creation of a statistics programme or designing a project.

externalised and acquired between organisations and it is possessed by people to implement the actions which correspond with the epistemology of possession. The fact that this research aims to study the production of knowledge production through the use of knowledge means this research should address how what is known (know-how and know-what) is used to implement the tasks. Then, in this thesis, the definition of knowledge provided by Cook and Brown (1999) is adopted and knowledge is seen as a group of concepts, procedures, norms and know-how that people have (epistemology or possession) and it is acquired, employed to solve a productive enquiry (epistemology of practice) and efficiently transferred in multi-site clinical trials.

## 2.4. Clinical trials defined as a knowledge-intensive project

The design, implementation and conclusion of a clinical trial depend to a large extent on the knowledge and use of this knowledge by the people working on it. Jensen and Sandstad (1998) considered that a clinical trial is a Knowledge Intensive Project (KIP). Later on, Azoulay in 2004 employed the term KIP to refer to the production of knowledge in a clinical trial. In a general sense, scholars have openly used the KIP term to refer to a project in which results depend strongly on the analytical skills and cognitive capabilities employed on the project rather than on the implementation of repetitive procedures (Jørgensen 2002) (which require, of course, the use of knowledge but not strong analytical skills). For example, the term KIP has been employed to classify projects outside the pharmaceutical sector like service projects (Larsen 2001; Skjølsvik et al. 2007; Brinkley et al. 2009; Roy and Sivakumar 2012), engineering projects (M. Jensen et al. 2007) and software development projects (M. Jensen et al. 2007; Patton 2007; Reich, Gemino, and Sauer 2012; Jørgensen 2002; Chi and Chen 2009; Tiwana and Ramesh 2001). All these projects have the use of knowledge work to design and/or execute tasks in common (Fong 2003). Under this logic, in this thesis, clinical trials are considered KIPs where the design and execution of the project lies on *the knowledge used by* epidemiologists, statisticians, physicians, doctors, nurses, technicians, monitors and people located across multiple organisations; and the *main knowledge product* is the evidence of the behaviour of a molecule or biological product in the human body or a population which achieves materiality in documents. Other sub-products are the protocols, medical reports,

The previous research about knowledge in KIP has focused mainly on intra-organisational projects and on understanding how firms and teams create knowledge over the course of the project, and how this can be stored and used in future projects. As a starting point, scholars have used the knowledge creation model proposed by Nonaka (1994) to study knowledge creation in KIP. This model assumes that individuals create new knowledge for the organisation by interconverting tacit and explicit knowledge, where individuals externalise, socialise, internalise and combine knowledge to create a new one (Nonaka 1994). However, a significant limitation of this approach is that it does not consider that knowledge is the result of an analytical activity. Therefore, the studies about KIP projects have only focused on the interconversion of forms of knowledge (tacit and explicit) and have left behind the actual understanding of how knowledge is employed in a project to obtain a result.

For example, Jensen and Sandstad (1998) developed a model to understand how pharmaceutical *companies* store their knowledge and information to operate with maximal effectiveness, so the generated knowledge stays in the organisational memory for further use. Nonetheless, this approximation has focused only on the externalisation of knowledge and its storage. In the context of project teams, Fong (2003) employed Nonaka and Takeuchi's model (1995) as a basis for understanding how knowledge is created in multi-disciplinary teams working on infrastructure development projects. In this model, knowledge creation is based on the interaction among team members to overcome social and cognitive barriers, where different knowledge-bases and experiences are combined to create new knowledge. Although this model considers the differences in the knowledge among team members and highlights how the combination of knowledge from diverse disciplines can lead to new knowledge, it pays less attention to the process of 'learning by doing' or 'creating knowledge by doing', which I consider critical in the process of producing knowledge products in KIP. In this sense, the studies about KIP projects have only focused on the interconversion of tacit and explicit knowledge and have left behind the actual analytical process of how knowledge is employed or not in a project to obtain a result.

In the case of multi-organisational projects, Yeh (2008) studied the creation of knowledge in outsourced KIP. He employed Nonaka's creation model to propose a framework to evaluate the production of knowledge in the boundaries between buyer



and supplier. The author considers that the interaction of people located in different organisations gives place to new knowledge, where people in one firm obtain new knowledge by being aware of a topic or issue related to the other organisation. However, similar to the previous research, this one was oriented to understand the transformation and transfer of tacit and explicit knowledge to create this awareness in the organisation, rather than to study the production of new knowledge as a product derivative of the implementation of the project where multiple organisations work. This fact appears to be a limitation of the emerging literature of knowledge creation in KIP to explain how the organisation produces knowledge products through the project.

Some reasons that explain this gap are that the literature about multi-organisational projects, KIP and the study of knowledge have oriented to understanding how firms can be more competitive and can use their knowledge as a competitive advantage to innovate. So, this focus has made scholars pay more attention to the processes of storing knowledge and using it in following projects rather than understanding the actual use of knowledge in the project. This gap is the one addressed in this thesis, and for this reason, I consider it necessary to present previous research on similar topics such as outsourcing.

## 2.5. Previous research about the outsourcing of knowledge activities

The literature on knowledge management has concentrated principally on generating an extensive range of theoretical frameworks and models to describe how the organisation as a whole should create, store, diffuse and use their knowledge to add value to the company (Dalkir 2005; Baskerville and Dulipovici 2006; Rubenstein-Montano et al. 2001). These approaches have been developed to answer questions like how an organisation can create new knowledge from data? How can new products be generated employing the organisational knowledge? And how can the core knowledge of an organisation be preserved? All these questions have implied an intra-organisational perspective.

Over the last 15 years, the interest in studying outsourcing activities to better understand how firms manage knowledge over the course of outsourced services or

projects has increased in the field of knowledge management. In recent years, some researchers on organisational studies employing a knowledge-based perspective of the firm and using concepts of the knowledge management theory have studied how sponsors should design the project to control the outsourced operations (Roy and Sivakumar 2011); how to promote innovation on the project's transition stages (Roy and Sivakumar 2012); how to mediate power in the outsourced relationship (Handley and Benton Jr 2012); and how to integrate global knowledge networks (Anderson Jr. and Parker 2013). Nonetheless, the literature has not addressed the entire flow of knowledge from the beginning to the end across organisations.

The reason for this turn is that, today, companies in a wide range of diverse industries are outsourcing or offshoring knowledge-based services to external firms. Thanks to the growth of information technologies, the outsourcing of knowledge-based services is becoming multinational. Outsourcing is increasing rapidly, augmenting between 2000 and 2015 in 43.4 billion US dollars in revenue (Statista 2015). Outsourcing includes a wide variety of activities, such as accounting (Risman, Aman, and Hamzah 2012), financial services (Blumenberg, Wagner, and Beimborn 2009; Currie, Michell, and Abanishe 2008), information technology (Dibbern et al. 2004), and research and development (Lowman et al. 2012).

Within the broad universe that composes the activities outsourced, some authors have focused the scope of their research to the outsourced activities that require high analytical thinking, use of knowledge and specialised skills to be implemented. These activities have been named knowledge process outsourcing (KPO) (Edvardsson and Durst 2014), which shares characteristics with the KIPs. The study of the KPO has focused on three broad areas of research. The first area addresses the motivation to outsource core activities. The second area has concentrated on the factors that affect the outsourcing (Lowman et al. 2012; Henley 2006). The third area has been about the knowledge management around outsourcing. This last area of study is divided into two lines of research: the first line is about how organisations manage their knowledge while they offer their services (Bustinza, Molina, and Gutierrez-Gutierrez 2010; Yan 2011; Zhao, Yim-Teo, and Yeo 2004; Mohannak 2013). The second line of research is the management of knowledge across organisations participating in outsourced projects (Samoilenko and Nahar 2011; M. Jensen et al. 2007) or in inter-organisational

relationships (S. Gupta and Polonsky 2014; Ngai, Jin, and Liang 2008; Matinheikki et al. 2016). The discussion in the following paragraphs is about previous research on knowledge management in outsourced activities.

Similarly to studies in Knowledge Intensive Projects (KIPs), previous research on outsourced activities has focused on understanding how outsourced firms create new knowledge and store it to make the firm competitive over the outsourcing (Yan 2011; Zhao, Yim-Teo, and Yeo 2004; Matinheikki et al. 2016) and the effect that the outsourcing has over the knowledge and competencies of the contractor (Lowman et al. 2012; Aban et al. 2008). For example, Zhao et al. (2004) argue that outsourced companies should pay attention to how to retain, utilise and create knowledge, to improve their corporate memory and core capabilities, and develop a culture to promote knowledge sharing across organisations. For these authors, in the organisation, knowledge should be created, identified, modified and then integrated into the company's processes in a continuous cycle of knowledge transfer, which should benefit all parties involved in the activity. On the same line of ideas, Yan (2011) considers that the implementation of a knowledge management system (an integrative software) within the organisation can support the acquisition, sharing, transfer, creation and application of knowledge in outsourced activities. For this author, the system designed to manage knowledge (IT infrastructure) should have an extensive knowledge warehouse to enable the knowledge acquisition and its posterior sharing. Once people acquire knowledge, this one can be employed in the business operations to innovate. Then, once again, the focus of research has been on knowledge and information storage.

The second line of inquiry within the management of the outsourced project has been the management of knowledge across organisations participating in outsourced projects or services. This line has received more attention than the previous one, where the transfer of knowledge and the identification of factors influencing the outsourcing have been the focus of the research. In this sense, multiple authors have argued the need to create a shared knowledge among the actors to enable the transfer (Samoilenko and Nahar 2011; A. K. Gupta and Govindarajan 2000), and the relevance of interpersonal relationships among people working on offshore knowledge-intensive projects have been pointed out (M. Jensen et al. 2007). During outsourcing activities, organisations

receive new knowledge transferred by the contractor. This new knowledge has to be integrated with their local knowledge and operationalised to create the product demanded by the contractor (Jackson and Klobas 2008). In this process, the outsourced organisation develops new organisational capabilities to manage all knowledge and information, the old one, the one received, and the new one, when the capabilities are oriented to learn, apply, merge, create, record and transfer the knowledge (Dalkir 2005). In this sense, different models have been proposed to manage knowledge across organisations. Samoilenko and Nahar (2011) proposed one model focused on the transfer of knowledge through training, where organisations share specific and general knowledge<sup>3</sup> about the business activity. Another model is the one proposed by Ngai et al. (2008) to manage knowledge across organisations participating in complex products and systems development projects. This model consists of three processes: Knowledge Acquisition, Knowledge Implementation and Knowledge Transfer.

## 2.6. Proposed model to study the knowledge flow between organisations and its use within teams

### 2.6.1. The model's building blocks

The creation of models to explain the management of knowledge within or across organisations has its roots in the literature of knowledge 'models, work and processes' (K. Grant 2011, 121); literature that has not been limited to studying outsourced activities. In this body of literature, different models have been proposed to study the flow, the storage and/or use of knowledge within the organisation, considering in some cases the interactions with other firms to acquire and transfer knowledge and information (Evans, Dalkir, and Bidian 2014). The principal objective of some of these models is to explain how firms manage their knowledge to create value for the organisation and to be more competitive and innovative (Maier 2004). I consider that three models of this literature proposed by Meyer and Zack (1996), McElroy (1999) and Ngai et al. (2008) are useful for studying the flow of knowledge, data and information

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<sup>3</sup> Zack defined general explicit knowledge as a broad knowledge that is independent of particular events, while specific knowledge or information refers to knowledge that is context-specific, where specific categories and descriptions should be provided (Zack 1999).

and its transformation within and across organisations to create new products and implement tasks (Table 1 provides a summary of the three models).

**Table 1. Comparison of three knowledge management models that have been employed to explain the management of knowledge at the intra-organisational level.**

	Meyer and Zack cycle (1996)	McElroy (1999)	Ngai (2008)
Model objective	To explain the in a firm how Knowledge Products are obtained	To manage Knowledge in a firm to solve enquiries	To manage knowledge across organisations participating in complex products and systems development projects.
Steps to manage knowledge	Knowledge Acquisition	Identification knowledge gap or problem	Knowledge Acquisition
		Research for information	
	Refinement	Use of knowledge	Knowledge Implementation
		Evaluation of the problem solution (loops to acquire knowledge)	
	Storage/retrieval	Integration to the organisation	Knowledge Transfer
	Distribution		
	Presentation		

Although each model has its complexities and each one addresses different processes in the organisations, these three models coincide mainly in three aspects:<sup>4</sup> the acquisition of knowledge, the use of knowledge in practice, and the transfer of results to internal or external users (Table 1). These three steps are critical to understanding

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<sup>4</sup> The scope of this section is not to discuss each one of the models; nonetheless, a summary of the steps proposed in each model are provided at Table 1.

the flow of knowledge, data and information in a firm. In the first step, people in the firm acquire knowledge, information and/or data from internal or external sources to implement the activities to increase their 'knowing' (McElroy 1999; Ngai, Jin, and Liang 2008). The other reason to acquire data and information is to analyse it and transform it into products, where people already know how to process this information and data (M. H. Meyer and Zack 1996). The acquisition of knowledge can have two directions. The first one is an in-out direction, where the firm searches for external knowledge and information because they need it. The second direction is the out-in direction, where the organisation is the receptor of knowledge transferred by an external agent.

The second element that these three models share is the use of the knowledge by people (acquired or the one that people already have) to execute actions. Either to analyse data or information (M. H. Meyer and Zack 1996) or as a part of the productive activity that the person is undertaking (McElroy 1999; Ngai, Jin, and Liang 2008). At this stage, the knowledge, information and data acquired are employed to execute the activities, produce the knowledge products, refine the data (M. H. Meyer and Zack 1996) or give a solution to the problems (McElroy 1999). And finally, the third aspect that these models share is the storage of results or lessons learned within the firm and/or transfer (McElroy 1999) to external organisations (Ngai, Jin, and Liang 2008; M. H. Meyer and Zack 1996), connecting the firm with another organisation. I consider that the attention McElroy (1999) gives to the existence of loops among the steps, and the evaluation of results is highly relevant because in clinical trials external actors and those doing the work are regularly reviewing the data, protocols and documents. Then, in each organisation, different cycles to gain knowledge exist, and these will be identified in the thesis.

It is important to notice that although these models have an intra-organisational focus, the actions of an organisation are implemented by the people working there. As these authors point out, people are the ones that learn, interact and produce knowledge. For these reasons, the attention on the models rests on people, their learning and actions, and then the results are scaled up at the organisational level to discuss how the organisation can enhance, store or get benefit from the knowledge produced and acquired by the people working in the firm.

The combination of these models to understand the flow of knowledge across organisations and the use of knowledge within the organisation in the execution of activities provide the conceptual framework to answer the research questions stated in this research. In this way, the basis of the model proposed in this thesis to answer the research question includes the steps shared among the three models compared before (see Table 1). The steps are the next ones: (1) The acquisition and search of knowledge, data and information from external and internal sources. (2) The use of knowledge (knowing) to solve the productive inquiry and evaluate results. (3) Results Storage and/or transfer of results to other organisations. These three steps are not linear. Firstly, there can be loops among steps as McEloyid (1999) indicated, especially between the acquisition of knowledge and its use. These loops are because the evaluation of the products can give as a result that the knowledge acquired was not enough or because people did not achieve their goals. Secondly, the acquisition of knowledge and its use in practice can take place simultaneously, so this must be considered as a variation of a linear model. Thirdly, it is necessary to keep in mind that once products are transferred, some activities do not finish; in some cases, intermediary information and data is sent as part of the project. Another element to consider is the number of organisations and the interdependency among them.

### 2.6.2. Inter-organisational dynamics in the model

As I have mentioned, a multi-site clinical trial is a project that takes place across multiple organisations, which can be in one or various countries. I consider it necessary to analyse the dynamics that take place at the intra-organisational level and inter-organisational level to study the process of producing the clinical evidence in a clinical trial.

Newell et al. (2008) addressed for the first time the study of the interdependencies among multiple organisations working on numerous projects (complex project ecologies) to develop and evaluate drugs and therapies. Nonetheless, their study did not address the interdependencies that take place in a single project where multiple organisations participate and the role of these interdependencies in the production of results, as it is the case of a single clinical trial. In the context of multi-organisational projects, Adenfelt (2010) pointed out in her research about multinational projects, that

knowledge is an input and output. The starting point for the project execution is the knowledge pre-existing in the companies, and the knowledge produced is an output shared over the course of the project. This argument coincides with the concept of interdependency proposed by Kumar. et al. (2009) to explain the relationship between activities executed in different departments or organisation in the same project. They based on the concept of interdependency initially coined by Thompson (1967), claimed that two actions are interdependent if the output of one operation in one department/firm is the input for another department, and there is a dependence on the results. Although the concept developed by Thompson (1967) was in administrative theory and organisational studies, this concept has been employed to conceptualise the dependency on results among organisations participating in a multi-organisational project and can complement the models discussed above.

At the inter-organisational level, the model that I propose considers the existence of interdependency among firms and their activities where the output of one organisation is the input of the other one to operate (Figure 1). In a multi-organisational project, more than two organisations can participate, then multiple interdependencies can be present in a project. The inclusion of the concept of interdependency allows us to understand the connections among organisations participating in a multi-organisational project, the dependency on results and the directionality on the transfer of products between firms. In this way, it is possible to follow, from the beginning of the project until its end, how organisations exchanged their results, and how the first knowledge, data and information was transformed through the network of actors into the evidence of the vaccine efficacy, efficiency, and safety.

This interdependency among products demands the constant acquisition and transfer of knowledge products across firms. The knowledge management literature about outsourced activities has paid particular attention to the study of the acquisition and transfer of knowledge. The research has focused on identifying critical factors that influence these two activities. I have identified three key factors highly reported in the literature of knowledge management in multi-organisational projects and outsourced projects, which impact the acquisition of knowledge and the transfer of knowledge, data and information to another organisation. The three factors are the sender-received dimension (in this thesis, structural dimension) through which knowledge, data and



information are acquired and transferred among firms; the knowledge-base of the people; and the permeability of individuals towards external information and knowledge. I consider it fundamental to include these three factors in the proposed model to study the flow of knowledge, data and information because they act as modulators of the knowledge flow across organisations and within organisations in the multidisciplinary project, as will be discussed in Chapter 4.

In the context of outsourced projects, the transfer of knowledge to create a shared knowledge among project workers is fundamental. Samoilenko and Nahar (2011) argued that the client is the one responsible for planning and conducting the training and transfer of specific and generic<sup>5</sup> information about the tasks to be implemented for the project. In this way, the supplier can have a deeper understanding of the project, and they can know what the contractor expects. Blumenberg et al. (2009) indicated that in IT outsourced relationships, the transfer of explicit knowledge has two dimensions. The first one is a content dimension, which includes the documents and training that contain the concepts required to reach a shared knowledge about the task and the project. The second dimension is a structural dimension, which consists of the structures that delimit the interaction between people and the transfer of knowledge. This dimension determines that people need to know who to contact to access or transfer information and what the hierarchies in the communication structure are (Blumenberg, Wagner, and Beimborn 2009). For example, not everybody in the firm is allowed access to top managers or to contact personnel in another firm directly. There are outlined structures to scale up information defined by the communication channels and rules to transfer the knowledge.

About this structural dimension, multiple authors have pointed out the importance of the sources and the transmission channels to acquire and transfer knowledge, data and information (Mandják et al. 2015; Alavi and Leidner 2001; A. K. Gupta and Govindarajan 2000; Anderson Jr. and Parker 2013). These two aspects are elements of the structure-dimension defined by Blumenberg et al. (2009). In the first place, the source can be located inside and outside the firm (Mohannak 2013). Sveiby (2001) proposed that there

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<sup>5</sup> Zack defined general explicit knowledge as a broad knowledge that is independent of particular events, while specific knowledge or information refers to knowledge that is context-specific, where specific categories and descriptions should be provided (Zack 1999).

are two primary sources in an organisation. The first one is the people who have the knowledge, and the second is the organisational structures (i.e. warehouse, databases), where information and data are collected. Similarly, channels are classified into personal (Mandják et al. 2015) or impersonal channels (Freiden et al. 1998; Sveiby 2001). Personal channels correspond to the interaction among people to acquire knowledge, where people socialise, externalise their knowledge and internalise new knowledge, and impersonal channels are databases, information repositories, e-training etc. Then, sources and channels can take the same shape; they can be personal or impersonal.

In some cases, the source and channels can be the same. For example, individuals transferring verbal information are at the same time the channel and the source of knowledge (Mandják et al. 2015). Alternatively, in other cases, humans are channels to transfer explicit information, like ‘boundary spanners’; they are intermediary people, carriers, that enable access to knowledge, information and data dispersed across multiple organisations, networks, and systems (Ansett 2005; S. Gupta and Polonsky 2014; Levina and Vaast 2014). They *do not have the knowledge or information*, but they search for it externally and transfer it to the organisation. So, the analysis of the structure employed to transfer and acquire knowledge must consider these differences.

Authors adopting a cognitive perspective of knowledge have suggested that people’s knowledge-base (basic skills, shared language and knowledge of scientific or technological developments) conditions the potential to acquire and introduce knowledge or information in the firm (Li et al. 2014; Nooteboom et al. 2007; Cohen and Levinthal 1990). The relevance of previous knowledge lies in the fact that the diffusion of knowledge is neither direct or straightforward; it requires a learning effort to be acquired (Akbar 2003). Memory works in an associative way, where people create new knowledge by establishing linkages with pre-existing concepts (Cohen and Levinthal 1990; Nonaka 1994). Different authors have discussed the relevance of overlapping or shared knowledge among people working together to exchange knowledge (Alavi and Leidner 2001; Tuomi 1999). Nooteboom (1992, 2000) inferred that people working in different environments interpret, understand and evaluate the word differently.

These differences in previous knowledge give place to the notion of “cognitive distance between people” (Nooteboom et al. 2007, 1017). It has been argued that on the

acquisition of knowledge, a long cognitive distance decreases the understanding among people, having a detrimental effect on the acquisition of knowledge (Nooteboom et al. 2007, 1017). Specific shared knowledge is needed for collaboration and knowledge acquisition. Therefore, if a sizeable cognitive distance exists between people, a learning effort is necessary to acquire knowledge and achieve a shared knowledge. In this order of ideas, in the context of multi-organisational projects, previous knowledge has relevance on the acquisition of knowledge and creation of shared knowledge.

Most of the discussions about knowledge-base have taken place at the firm level, where a knowledge-based theory of the firm has been developed (Nickerson and Zenger 2004; Kaplan et al. 2001); this theory that has its roots in the resource-based view of the firm. The primary objective of this theory is to integrate the knowledge residing in the organisation through a series of changes in the organisational structures to manage it (R. M. Grant 1996). Nonetheless, in the specific case of the influence of knowledge on the acquisition of knowledge in a project, the scope is entirely different to the one addressed in the knowledge-based theory, in which is studied how to optimise the use of knowledge present in the organisation (Nickerson and Zenger 2004). In the study of knowledge acquisition among firms, the term 'knowledge-base' refers to the previous knowledge that a person has (or group of people in a firm has) and how this previous knowledge allows them to acquire new knowledge, as discussed above. Therefore, it is essential to differentiate between knowledge-based theory and the concept of knowledge-base introduced here. In this research, the focus is on how previous knowledge influences the acquisition of knowledge, which is the aspect related to the knowledge flow.

The third factor to consider in the acquisition of knowledge, data and information is the permeability of people towards external information and knowledge. Gupta and Govindarajan (2000) indicated that people's motivations to acquire and receive knowledge influence the acquisition of knowledge. For these authors, the "not-invented-here" syndrome, proposed firstly by Katz and Allen (1982), prevents the flow of information to the organisation and becomes a barrier to acquiring knowledge. This syndrome takes place where recipients consider that the information and knowledge transferred to them indicate that the sender is more competent. This syndrome happens if receivers want to diminish the value and relevance of the transferred

knowledge. Some authors have suggested that this attitude towards external knowledge can be considered a psychological issue, as it is individual-based (Grosse Kathoefer and Leker 2012), which prevents the acquisition of relevant knowledge or information for a project and has a negative consequence in the organisation (Lichtenthaler and Ernst 2006). In contrast to this syndrome, Menon and Pfeffer (2003) suggest that in some cases the use of transferred knowledge is preferred by some firms rather than using the knowledge generated internally, which they may consider being less valuable or relevant, then, peoples are more receptive to acquire and use external knowledge. Although both positions could have adverse consequences for teams and organisations, what is critical to this discussion is teams' permeability to acquire and use the knowledge received, which can create a barrier to the knowledge flow.

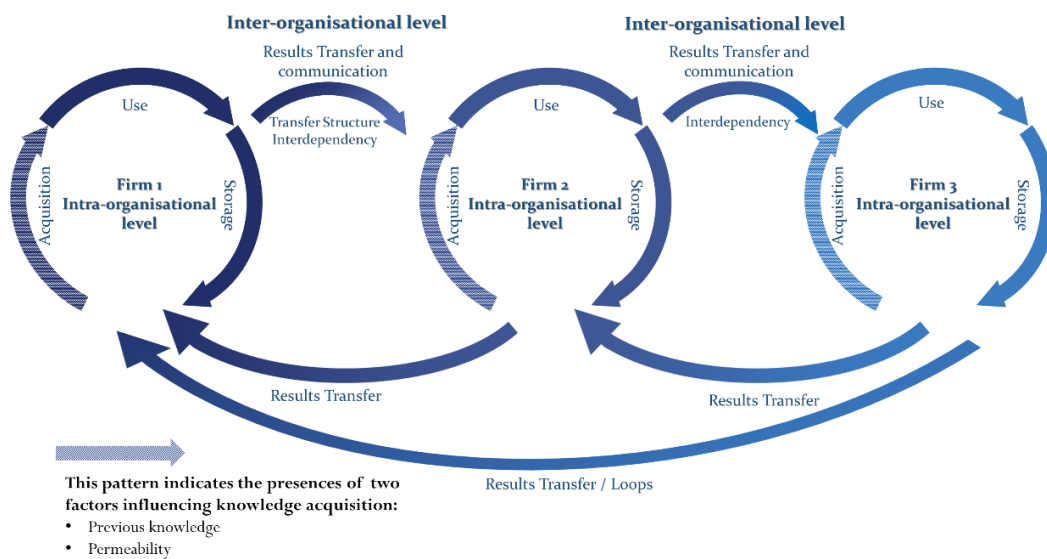
As I presented above, teams and their members might be selective toward external information being sometimes closed entirely to receive external information and knowledge, or at other times, they are entirely open to receiving and using external knowledge. I use the term 'permeability', making an analogy between the selectivity of personnel at the teams and the process employed by the cells to control the absorption of polar and big molecules to maintain the cellular composition (Cooper 2000). A cell is more or less permeable to external molecules opening or closing specific transmembrane proteins that control their entrance. Based on this analogy and the information presented, I suggest that in the teams there can be different degrees of permeability to the external information, which is mediated by people's motivations to accept (or not) the knowledge and information coming from outside its boundaries. Then, I propose two categories of analysis to study the permeability: high permeability and limited permeability. Teams are highly permeable or non-selective toward information and knowledge if people do not present a high resistance to external information; this is the case if teams prefer external knowledge rather than internal knowledge or do not question the external one. On the other hand, people are less permeable if they doubt the validity of the external knowledge, as is the case in the "not-invented-here" syndrome, where these teams select only information or knowledge that they consider pertinent or valid, or avoid the use of external information. I will use these two levels of analysis to determine how receptive and

permeable people were respecting external information, and identify the reasons that lead to these positions to accept it or not.

### 2.6.3. The proposed model and its use to answer the research questions

In conclusion, Figure 1 summarises the proposed model to answer the research questions and study *the flow of knowledge across organisations and its use to produce the productive enquiries*. The model has its roots in the literature of knowledge ‘models, work and processes’ (K. Grant 2011, 121) (Table 1). And it was complemented with the concept of interdependency, and critical factors that seem to influence the acquisition and transfer of knowledge: people’s knowledge base, the structural dimension to transfer knowledge and the permeability of people towards external knowledge.

**Figure 1. Conceptual model proposed to study the flow of knowledge across organisations and its use within the firm. Graphic made considering a hypothetical scenario of three interdependent organisations working on the project.**



The research questions elaborated in this thesis were built on the premise that a clinical trial is a multi-organisational project, where the sponsor and clinical sites produce interdependent knowledge products. The first product is the clinical protocol designed by the sponsor; the second product is the clinical data (obtained by the research using their knowledge, the protocol and information transferred by the sponsor). The use of this model will allow me to compare among the cases studied the

flow and use of knowledge in the project activities, identifying trends and the differences among cases and organisations of the same type (Sponsor vs Sponsor, Site vs Site) in each one of the steps.

The first research question of this project is ***how does the sponsor integrate internal and external knowledge, data and information to design the clinical protocol?*** Using the proposed model to answer the research question, I will analyse, at the intra-organisational level, how the sponsors accessed information, data and knowledge required and combined it with previous results to produce the protocol. In this analysis, I will discuss how previous knowledge, or the lack of it, influenced the acquisition of knowledge and how the permeability of the clinical team towards external knowledge defined what knowledge was used or not in the protocol design.

The second research question of this thesis is ***to what extent does the knowledge-base of people working on the project, the structure designed by the sponsor to transfer knowledge, and the permeability of the research sites influence the transfer/acquisition of knowledge in the research sites?*** This question is about the interdependency between the sponsor and how the identified factors affect the acquisition of knowledge by the research sites. The answer to this question includes the sponsor and the site perspective. Firstly, the answer includes how the structure created by the sponsor to transfer information to the sites enabled (or not) the knowledge acquisition by the research sites, and how the presence of intermediary organisations influences the transfer process. Secondly, in this chapter, how the previous experience that people had in the clinical sites influences the acquisition of new knowledge is analysed. For this, it will be of the knowledge-base of the people receiving the new knowledge and information. I will identify the experience and training of the personnel and its relation to the acquisition of new knowledge and the creation or reinforcement of the conceptual basis and practices to execute the project. The evaluation of this factor is relevant, especially for studying new organisations without experience conducting clinical research. In this way, from these organisations, it will be possible to learn how people use their previous training or professional background as a tool to acquire new knowledge and close the knowledge gaps before initiating the project.

Finally, the model proposed will be employed to answer the third research question of this thesis, that is: *How is knowledge employed in the clinical research sites to produce the clinical data and transfer it to the sponsor?* This question takes us to the intra-organisational dimension of the research site and addresses the use of the acquired knowledge from the sponsor and the knowledge that already resides in the clinical team to execute the clinical trial and produce and transfer the clinical data. The production of the clinical data demands multiple activities from the personnel. Therefore, to answer this question, what specific knowledge was employed in each one of these activities, the relevance of the previous knowledge to implement new procedures, and how people had to develop new know-how to solve the productive enquiries and produce the clinical data will all be discussed.

I discussed above how previous research on KPO has focused on specific aspects of the outsourcing. Nonetheless, scholars have not researched the flow of knowledge across the actors engaged in the outsourced activities, and the use of the knowledge within each firm to execute their task in the project. This thesis contributes to the study of knowledge management in multi-organisational projects, answering the research question stated above, studying for the first time the flow of knowledge over the course of a project and its use within the organisation to meet the project goals. Answering these research questions, I contribute not only empirically to the study of the production of clinical evidence in multi-organisational clinical trials, but also theoretically, using the literature of knowledge management models in a novel way. Firstly, proposing a model to study the knowledge flow across organisations in the context of a project. Secondly, evaluating the model introduced above for the first time along a chain of activities that take place across different organisations dispersed geographically, where various forms of interdependencies exist.

#### 2.6.4. Considerations

Some people could consider that the results of a clinical trial are the result of the co-creation of knowledge involving all the different organisations along the activities value chain of this product. To say that knowledge is co-produced, it is imperative that multiple stakeholders *engage and integrate multiple perspectives* that shape the understanding, and processes of knowledge generation and use (Rycroft-Malone et al.

2016). This condition is not met in the implementation of a clinical trial, where each organisation has clear responsibilities, and the boundaries between firms on the knowledge production are defined, and only the sponsor takes the critical decisions of the project.

A clinical trial is a project where the only organisation responsible for the project is the sponsor. Yes, personnel at the research sites use their knowledge to produce the data, which is vital in the project, and I will be discussing how they do it and what knowledge they use. Nonetheless, this is their responsibility as an outsourced organisation to supply a service; service that demands the use of knowledge, but in the final results these providers are not allowed to take part, and their perspective is not integrated to generate the final results (new knowledge). Suppliers have reduced interference on the project design and data analysis, as this thesis will evidence. Even though when principal researchers at the sites tried to contribute to the project design, their comments, in some cases, were not accepted easily, which clearly indicates the boundaries on responsibilities in the project and until which point they could or could not contribute to the project. There are few cases where the sponsor decides to challenge the model proposed in the industry and decides to involve the principal researchers of the sites in the project design and analysis (as one of the cases illustrates). Nonetheless, this is an isolated case that I cannot generalise to argue that the results of a clinical trial are the product of the co-creation or co-production of knowledge. Then, in a strict sense of the word and analysing a recent definition of knowledge co-production, it is clear that the result of a clinical trial is not the result of a co-production of knowledge. The results among organisations are interdependent but not co-produced, and for this reason, this thesis will focus on the flow of knowledge and knowledge products across actors to achieve specific goals and finally produce the clinical data.

## 2.7. Summary

In summary, in this chapter, I have presented the research questions of this project and the theoretical framework to provide an answer to them. In the first place, I showed how, over recent years in Latin America, the landscape of the clinical trial industry has changed because of the emergence of new actors like CROs and SMOs. These actors



are reshaping implementation of the protocols and the relationships between the two traditional organisations in a clinical trial, the sponsor and the research sites. In this changing landscape, this chapter presented the research that has been conducted to study the production of knowledge in clinical trials, and it elucidated the gap that exists to understand the flow of knowledge over the course of the project in this new multi-organisational project landscape. Based on these gaps, I introduced the central research question of this thesis. Then, I introduced the three sub-research questions of this project, which have their origin on the interdependency of two knowledge products in the clinical trial, the research protocol and the clinical data.

The fact that the principal object of study in this thesis is knowledge, in the second section I presented the definition of knowledge and the reasons why I adopted the epistemology of practice and possession proposed by Cook and Brown (1999). This approach of knowledge brings together the cognitive perspective employed in the literature of knowledge management, and the study of the use of knowledge in action.

In the third section of this chapter, I defined clinical trials as Knowledge Intensive Projects and presented the previous research on this topic in relation to the production of knowledge. Because outsourcing seems to be a repetitive action in multi-organisational projects, and in multi-organisational clinical trials it is a constant.

In the fourth section, I introduced the previous research about the outsourcing of knowledge activities, and the main research areas that have emerged to study these activities to then place this research on the research of the management of knowledge in outsourced tasks. In this section, I did a literature review of previous studies of knowledge management in outsourced activities and the gaps in these research studies mainly on the creation of knowledge in this context. Based on these gaps, in the fifth section I introduced, from the literature of knowledge, 'models, work and processes' (K. Grant 2011, 121): key models that have been proposed to study the flow, the storage and/or use of knowledge within the organisation that I consider useful to explore the flow and use of knowledge in multi-organisational projects. Based on these models and a review of previous studies on the transfer and acquisition of knowledge in outsourced projects, I proposed a model to answer the main and sub-research questions of this thesis. The model has two levels, one inter-organisational level, and one intra-

organisational level. The first level addresses the interdependency of knowledge products across the organisation, considering three factors that influence the transfer and acquisition of knowledge and knowledge products across project teams. The second level addresses the production of the knowledge products within the teams and how knowledge is employed to meet the project goals, making a particular emphasis on how acquired knowledge and previous knowledge is combined in action to produce the productive enquires. I consider that the proposed model with the identified factors is robust to study the production of knowledge products (clinical data, protocol, reports) and the flow of these products, and different data, knowledge and information among various organisations (sponsor, CROs, clinical sites) in multi-site clinical trials.

# Chapter 3: Research Design, Data Collection and Analysis

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## 3.1. Introduction

In this chapter, I outline the research design, the qualitative data collection methods employed, and the analytical framework. In this way, I explain why I chose a multi-case study perspective and the rationality behind my methodological decisions. This chapter has six sections. In the first section, I explain the research design of this project, and I discuss why I selected a multi-case study as the method employed in this research and the procedure to choose the cases, and I introduce each one of the three cases. In the second section of this chapter, I present the methods employed to collect the data. I mainly discuss why I conducted semi-structured interviews and how I did the fieldwork to cover the three cases in the three countries, pointing out the challenges and limitations that emerged over the fieldwork. The third section discusses the strategy employed to analyse the data collected using a framework approach and the challenges and decisions implemented to translate the data. The fourth part addresses the ethical considerations of this research. The fifth section is a reflection of my position as a researcher. The sixth section is the summary of this chapter.

## 3.2. Research design

### 3.2.1. Comparative case studies

In the last chapter, I discussed how past research on multi-organisational projects have not addressed the use of knowledge within firms and how it flows across multiple organisations participating in multi-organisational projects at the same time. In those cases where research and theory are at early stages, researchers have argued that a case study research design is particularly suitable (Bennasat, Goldstein, and Mead 1987) to advance on the field of studies. This method helps to capture a rich array of contextual data, and it is possible to study the phenomenon from the perspectives of diverse participants using multiple levels of analysis. In this way, previously unknown topics

can be understood, addressing complex processes. As Bhattacharjee (2012) indicated, a case of study is a method “well-suited for studying complex organisational processes that involve multiple participants and interacting sequences of events” (underlined added), as is the case for this project. Therefore, a case study research allows the researcher to unravel a complex set of factors and relationships, making the research dynamic, asking interviewees more questions between the various stages of the research project (Verschuren 2003).

Nonetheless, those taking a positivist approach have criticised the use of a single case of study because of the low generalisability of the observed associations to the population (Verschuren 2003; Mookherji and Lafond 2013; Gray 2009). The use of **comparative case studies** has been proposed to address this issue, where two or more cases are covered to analyse the studied phenomenon across cases and within cases, so results and knowledge obtained from causal questions (How and Why) can be more generalisable (Bennasat, Goldstein, and Mead 1987). For this reason, this thesis follows a comparative case study design, with in-depth analysis of *three vaccine clinical trials* (three cases) to conduct a comparative analysis across cases and conduct a detailed analysis of each case. In this way, the richness of the case study method was conserved, and additional comparative analyses were performed. For this reason, I considered that the comparative case study method was the most valuable methodology for exploring and understanding the dynamics in the flow and use of knowledge in multi-site projects, in this way, addressing the complexity and dynamism of this study.

According to Bhattacharjee (2012), the quality of a research design can be assessed regarding four primary attributes: internal validity, external validity, construct validity, and statistical conclusion validity. A good design has equilibrium between internal and external validity. The internal validity or ‘causality’ evaluates the direct association between independent and dependent variables, aiming to restrict the influence of external factors associated with the research context. Therefore, researchers must control the effects of extraneous variables, although this is not always a hundred per cent possible. The second attribute, external validity, refers to the possibility of extending the results from one context to the population. This validity is obtained evaluating multiple samples to attain a better picture of the population. The research

design that I employed aimed to find equilibrium between these two attributes to have a robust project and data to answer the research question.

The process to achieve internal and external validity is named ‘elimination technique’, which consists of decreasing extraneous variables by holding them constant across treatments (cases) (Bhattacharjee 2012, 38). The elimination technique to select the cases and achieve the equilibrium had two components. Firstly, to achieve **external validity**, I decided to adopt a comparative case study method between three clinical trials in different stages of development. Comparing among cases, I expect to find enough evidence that allows me to elucidate key points that positively or negatively influence the flow of knowledge and also allows me to understand, within firms, how pre-existing knowledge and the one received converge to implement the productive enquiries.

Secondly, in this research project, to accomplish **internal validity**, I identified one disease for which there were more than one vaccine/medicine candidate under development, and sponsors implemented the clinical trials in Latin America. In this way, I guaranteed the embeddedness of the selected cases in the same context; specifically, under similar market pressures, the same initiative to boost the development of the product,<sup>6</sup> and the same epidemiological conditions. The three cases selected are not exactly identical; variations exist among them, which is expected in social science and must be considered in the analysis and allows the achievement of external validity. However, if I had included clinical trials for cancer, diabetes, or other chronic disease, the comparisons and analysis would have been more complicated because of the intrinsic difference between trials to evaluate drugs and vaccines.<sup>7</sup> This large variance among cases would have blurred the inference and comparison. Of course, part of my analysis consisted of identifying the interaction of the cases with their surrounding context, but with the proposed design, the objective was to select

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<sup>6</sup> This makes reference to the demand of evidence to prove the vaccine’s efficacy and the work led by the DVI (Dengue Vaccine Initiative) to harmonise the requirements to introduce the first vaccine candidate in endemic countries. So, in this sense, the three vaccines are under this same institutional dynamic.

<sup>7</sup> For example, vaccine trials demand more volunteers than drugs trials, recruitment strategies are different; to evaluate new drugs in Latin America, physicians enroll their patients, in a vaccine trial, subjects are not patients and are enrolled using massive diffusion strategies (Chapter 6).

cases in a similar context to make more evident the difference or similarity between cases.

Regulations are different in the three countries selected (Brazil, Colombia and Mexico). Therefore, to address this issue and achieve internal and external validity, I chose the countries based on the number of cases evaluated in the country, and at least one case should have a presence in the three countries. Selecting a case with a presence in multiple countries, I could contrast if variations in the local regulations in any way influenced the execution of the same project in each country. Having more cases in the same country, I could compare and identify the influence of the local regulation on the implementation of different projects, allowing me to identify and control the effects of this extraneous variable. Therefore, with this design, I aimed to find an equilibrium between internal and external validity having a better resolution on my results.

### 3.2.2. Selecting the cases

The three cases chosen in this research correspond to the clinical evaluation of three dengue vaccines in Colombia, Brazil and Mexico. The process to select the three cases was divided into two steps. In the first step, I revised the literature about drugs and vaccines under research that summarised the pipeline of products under development to prevent and treat infectious disease. These documents include published reports by consortiums supporting the development of new vaccines like those supported by the Bill and Melinda Gates Foundation and the Drugs for Neglected Diseases (DNDi). One key document was 'A report on the prevention and treatment of disease through vaccines' (America's Biopharmaceutical Research Companies 2013). The data collected indicated that 137 vaccines aiming to prevent infectious disease were under development. Thirteen infectious diseases had more than two vaccines under development (Table 2), and four global alliances existed to speed up the development of vaccines and treatments for malaria, tuberculosis, HIV and dengue.

**Table 2. List of infectious diseases for which existed vaccine candidates under clinical evaluation in 2013. In the last column are the countries in the Americas, where the trials took place.**

<b>Disease</b>	<b>Phase</b>	<b>Candidates</b>	<b>Countries where vaccines were evaluated in the Americas (Clinicaltrials.gov)</b>
Anthrax	Phase II	5	The USA (4)
CMV	Phase I and III	2	The USA (2) Canada (1)
<i>Dengue</i>	<i>Phase I, II and III</i>	8	<i>The USA (8), Mexico (1), Panama (2), Honduras (1), Puerto Rico (3), Colombia (2), Peru (1), Brazil (2), Dominican Republic (1),</i>
H5N1	Phase I, II and III	17	The USA (17)
Hepatitis B	Phase I and III	2	The USA (2)
Hepatitis C	Phase I and II	3	The USA (2), Panama (1)
Herpes simplex virus (HSV) infection	Phase I and II	3	The USA (3)
HIV	Phase I and II	25	The USA (20), Argentina (1)
Malaria	Phase I, II and III	4	The USA (3)
<i>Meningococcal</i>	<i>Phase I, II and III</i>	6	<i>The USA (5), Mexico (1), Panama (2), Dominican Republic (1), Colombia (1), Argentina (1)</i>
Prevention of Clostridium difficult	Phase I and III	3	The USA (3)
<i>Prevention of herpes zoster</i>	<i>Phase III</i>	2	<i>The USA (2), Brazil (1), Mexico (1), Canada (1)</i>
Tuberculosis	Phase I and II	4	The USA (3)

The second step to select the cases of study focused on the thirteen diseases identified that had new products associated. This step consisted of consulting the database clinicaltrials.gov<sup>8</sup> to determine the clinical trials that had/have been conducted for

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<sup>8</sup> Managed by the NIH of the USA, where sponsors around the world voluntarily provide information about the clinical trials that they are running.

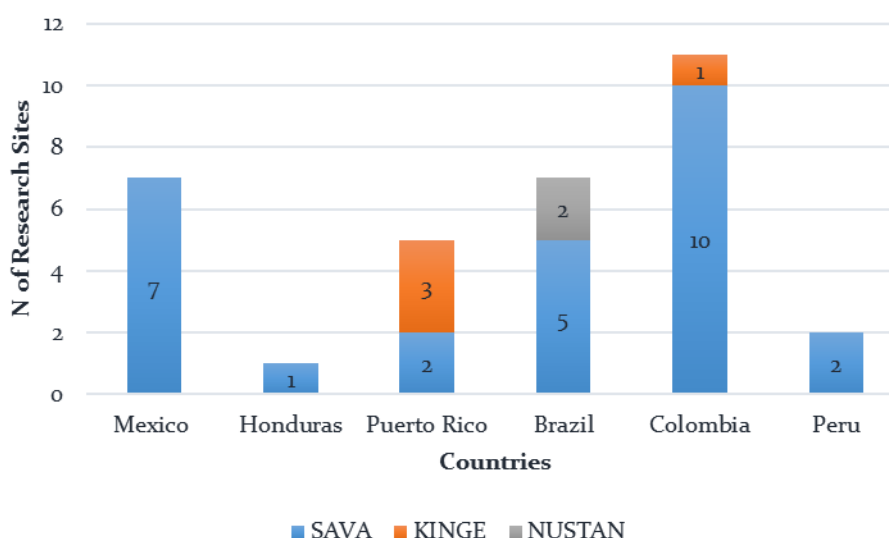
these products, and, more specifically, if those trials took place in Latin America. As it is possible to see in Table 2, the vaccines to prevent herpes zoster, meningococcal infectious and dengue fever were the only vaccines evaluated outside the USA and include at least two Latin America countries. The rest of the vaccines have been assessed mainly in the USA or Europe and Africa (information not provided in Table 2). Of these three vaccines, I selected the dengue vaccine candidates as cases of study because at least two of the vaccine candidates were evaluated in the same country (Panamá, Puerto Rico, Colombia and Brazil) compared with the other three options, which allowed me to make comparisons between cases in the same country.

Once I decided on the disease, I identified the cases included in the study. For this, I reviewed the information published in the Dengue Vaccine Initiative reports (DVI 2013), which indicated the stage of development of each one of the vaccine candidates. Of the eight candidates under development, four were on pre-clinical evaluation in the USA. One vaccine was evaluated in the USA for the clinical trial phase I. KINGE was evaluating its vaccine in Phase III in the USA and Colombia and the NUSTAN vaccine was evaluated in phase II in Brazil. SAVA evaluated its vaccine in Phase III in five countries in Latin America (Colombia, Mexico, Brazil, Puerto Rico, Perú). Therefore, of these eight options, I decided to study the three vaccines that were in the latest stage of clinical evaluation (phase II and phase III), and trials included Latin America countries. One of the advantages of these three cases is that each one has a different level of complexity in the number of actors and kind of organisations that are part of the project. In the NUSTAN case, the sponsor and the research sites had a direct communication, and there were no intermediaries present. The figure of the CRO emerged in the KINGE case, mediating between the site and the sponsor. In the case of SAVA, a CRO and SMOs were outsourced, which represents one of the most complex structures to execute the project. However, this case represented an excellent opportunity to study the changing landscape to implement clinical trials in Latin America. Over the fieldwork, I identified differences between the cases that were not anticipated over the project design because this information was not available in the published papers and reports. Nonetheless, these differences were very important to understand how the structure to transfer information influenced the flow of knowledge from the sponsor to the site over the transition period before the transfer started.



Once I selected the cases, the next decision was to choose the countries to visit to collect the research data. This decision was made based on the number of research sites located in each country and the budget available to conduct the fieldwork. For this, I created a sub-database in Excel with all the information about the cases, including the name of the vaccine, the sponsor, the clinical phase, clinical trial code in the database, the studied population, the country and state department where the trials took place. Until 2014, to evaluate SAVA, KINGE and NUSTAN vaccines, sponsors had registered 38 clinical trials in the database [clinicaltrials.gov](http://clinicaltrials.gov), and 30 trials had been conducted partially or entirely in Latin America. At that time, vaccines were evaluated in seven Latin American countries, six Asia-Pacific countries, the USA and Australia. More than 90 academic, public or private research organisations had participated in the global trials, where 12 were in Latin America. With this data, I could identify the number of studies implemented in each country and how many research sites were part of the project, as is presented in Figure 2.

**Figure 2. The number of research sites per country outsourced in each one of the cases of this research.**



Using this information, I decided to do the fieldwork of this investigation in Colombia, Brazil and Mexico. I selected Brazil and Colombia because two of the three candidates were evaluated there. I chose Mexico rather than Puerto Rico because Mexico had more sites, it was cheaper, and it has significant relevance in the clinical trial industry. Mexico is the second market to conduct clinical trials in all Latin America after Brazil. In this selection process, I also considered the life cost in each one of these countries and the

possibility of affording the fieldwork, which included the trip among countries and within the country to visit the research site. The result of this systematic approach to identify the case studied and select the countries to conduct the fieldwork allowed me to make comparisons within and across cases in different countries. Either comparing the same case between three countries or different cases within the same country (horizontal and vertical analysis).

### 3.3. Methods of data collection

Multiple methods of data collection are employed in a multiple case study design, including interviews, observations, pre-recorded documents, secondary data, surveys etc. (Bhattacharjee 2012, 93; Edvardsson and Durst 2014). Arksey and Knight (1999) suggest that interviews allow in-depth exploration of the meaning and understandings that people have about their context. My thesis aims to study how people in the organisations acquire, use and transfer knowledge when they are participating in a multi-organisational project to achieve the project goals. Attaining this objective is complex because of the presence of multiple organisations and the need to establish a design that allows us to grasp the dynamic, and cognitive dimensions of this research. For this reason, qualitative research was considered more appropriate to address the complexity and dynamism of this study. For this project, primary data were collected using semi-structured interviews with open-ended style questions<sup>9</sup> (Appendix 1.). Using these questions, I could capture what researchers, technicians, monitors and sponsors wanted to express in their own words while still following an ‘informal’ structured dialogue.

As Arksey and Knight (1999, 32) suggest, interviews are potent tools that encourage people to express their tacit perceptions, feelings and understanding about their world. This method favoured face-to-face situations, enabling rapport between myself as a researcher and the project’s member in their settings (Blaikie 2010). Semi-structured interviews allowed me to get into people’s memories about the project and bring up elements of what was, for them, being part of the project design (sponsor) or execution (site’s personnel and monitors). With in-depth interviews, I could pinpoint those

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<sup>9</sup> The number of interviews and personnel interviewed is detailed below.

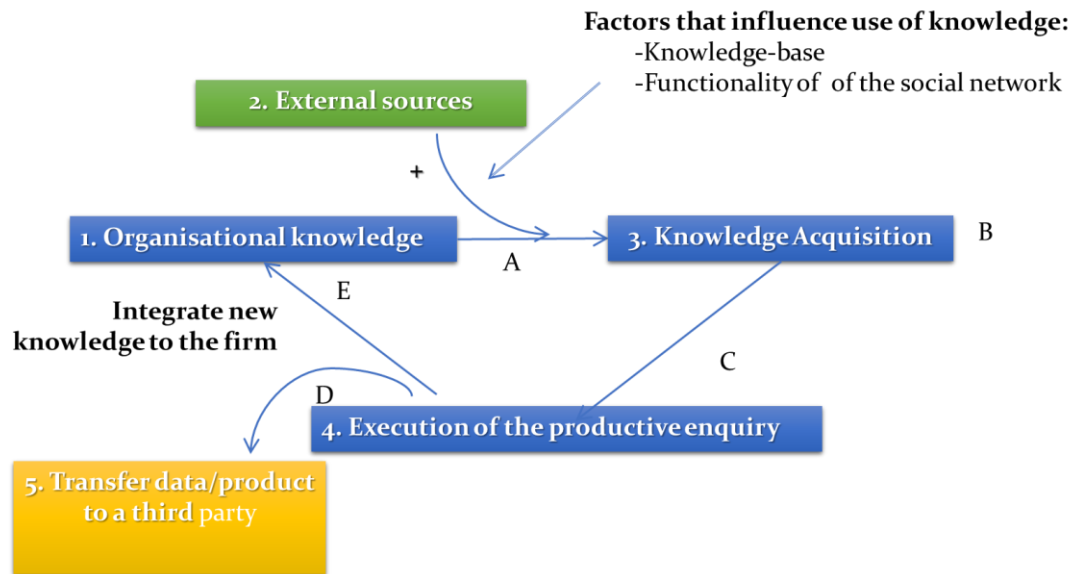
specific elements related to the acquisition and implementation of knowledge to make them aware, to some extent, about what they had gone through. The people interviewed could reflect on the implicit and 'normal' way of doing new things and make them explicit. The use of semi-structured interviews enabled the identification of similar answers to contrast them; this type of interview also gave the opportunity to find unforeseen information.

However, like it has been pointed out by different authors, interviews can have some limitations. The context of the interview and their unconscious bias can influence interviewees (Diefenbach 2009; Boyce and Neale 2006). I recognise that these are some limitations that could have been present in the data collection. In the first place, people can be unreliable witnesses of their own past experiences and activities; they can portray themselves as leaders or that they had everything under control. For example, in a few cases, principal researchers interviewed were more interested in narrating their successful story implementing the clinical trial. Then, when I identified that information had a substantial content of pretence and egocentricity, I counter-questioned about the failures reported in the papers or that were told by other researchers or I rephrased the question to create a balance in the information. In this way, I could get an authentic account of the data. The ability to detect these biases improved with experience. So, initial interviews could have less counter-questioning, and, therefore, their analysis required greater caution. Also, all interviews were contrasted with the answers of other interviewees (details below).

Over the interview, in addition to the questioner, I had a map of the theoretical model that I had elaborated to study the knowledge flow (Figure 3). Over the course of the interview, using this map, I assured I had covered each one of the steps in the model. The fact that I was using a semi-structured interview format allowed me to go deeper into specific topics that emerged over the interview, in this way, getting a rich insight about the project. Model and concepts discussed in the theoretical framework were the base for these interviews, and they followed a chronological format. The interview began with questions regarding the personal and institutional antecedents before moving to operational issues like the acquisition of knowledge or the execution of the project, the practices to implement the activities and the interaction with other members of the project. Because I'm studying multi-organisational projects, for the

interviews, I developed a question schedule for each actor involved in the project, one for the sponsor and another one for the personnel in the research site, including questions about the topic and the concepts under research. Nonetheless, because the model proposed was similar for both organisations, aspects like the use of knowledge, access to information and transfer of data and knowledge were asked in both interviews.

**Figure 3. Map employed to follow the flow of the interviews.**



I conducted 65 interviews, of which 49 were directly related to the cases of study (Appendix 2.) Of these interviews, 11 were about the KINGE case, 32 about the SAVA case, and five about the NUSTAN case. Each interview lasted between 40 minutes and two hours. Interviews related to the cases included five members of the sponsors (3 SAVA, 1 KINGE, 1 NUSTAN), three CRO monitors (2 SAVA, 1 KINGE), six project managers (3 SAVA, 2 KINGE, 1 NUSTAN), three SMOs directors working for SAVA, eight principal investigators (6 SAVA, 1 KINGE, 1 NUSTAN), eight sub-researchers (6 SAVA, 1 KINGE, 1 NUSTAN), three social workers (SAVA), two quality managers (1 KINGE, 1 NUSTAN), one laboratory technician (SAVA), two health promoters (SAVA). The other interviews included regulatory agencies, ethical committees and members of the wider clinical research industry in Colombia, Brazil and Mexico, like clinical trial associations, which allowed me to understand the context of the clinical trials in these

countries. Additionally, in Mexico and Brazil, I attended annual conventions of the national clinical trial associations, where I interacted with leaders of the clinical trial industry. This information was useful to understand the debates in the communities in each country, the local regulations and the system, and the separation between the different actors regarding their participation in the debate. However, these interviews were not employed in the analysis because the objective of this trial was the production of clinical results over the course of a project and it does not have an objective to study the industry or, exclusively, the regulation. Also, I took an introductory course on Good Clinical Practices at the University of Edinburgh so I could better understand the concepts employed in clinical research and, in a way, the learning process experienced by the personnel at the research sites.

As I mentioned before, other methods like participatory observation and surveys could have been used to collect data about a case of studies. However, these two methods of data collection were not suitable for this research. Although an ethnographic work could have been appropriated to investigate the practices of the personnel in the research sites to implement the project and the use of knowledge, this method was not suitable for three reasons. The first one is that it was not possible to conduct an observation about the initial stages of the project because the recruitment of participants, vaccinations and active evaluation of participants had passed. Therefore, personnel had a lower peak of work. The fact that my fieldwork took place in these low peaks of work was positive for my research because personnel at the site had more free time to answer questions. Interviews were more in-depth and not rushed (KINGE and SAVA cases). The second reason is the difficulty to get access to the research sites to observe the project implementation if they are evaluating volunteers. All information in clinical research is confidential, and every person that has access to the volunteers or is present during the project execution must be approved by the local ethical committee, even though monitors that are part of the project are not allowed to have contact with the volunteers or be present during the medical consultation. Therefore, getting this access and approval by each one of the ethics committees of each case studied could have taken around one year, so interviews were more suitable for collecting data. Finally, the fact that I decided to implement a multi-case study with locations in multiple countries implied that I had to be strategic and flexible with the

use of time to travel and collect the data. An ethnographic method does not allow this flexibility because it is necessary to spend more time at each site creating links with the personnel, building a relationship and collecting data.

As for surveys, this method is more related to quantitative studies. This research focuses on understanding a process of acquisition, use and transfer of knowledge; for this reason, I was more interested in the narratives of researchers about their learning process, the interaction with other actors, and the use of knowledge to design the project or implement it. So, in-depth semi-structured interviews allowed me to capture the sequences of the story, the interdependency among organisations and the flow of the research project. Surveys could have been useful if the studied cases had had a larger number of research sites. Nonetheless, this data had to be complemented with interviews to address the complexities and unique aspects of each case.

### 3.3.1. Fieldwork and some limitations

Scholars have argued that the selection of interviewees must be guided to a great extent on the personal involvement of the person in the phenomenon under investigation, the power and influence of the people within the organisation, and their ability and willingness to answer the research questions adequately and accurately (Bhattacharjee 2012; Diefenbach 2009). Therefore, before initiating any data collection, the first step was to identify key people in each one of the cases of study to access to them. Once I determined the cases and the countries to conduct the fieldwork I created a database with the names and positions of the people working in each one of these clinical trials. To achieve this, I employed the information published in the database [clinicaltrials.gov](https://clinicaltrials.gov), in reports of the advancement of the vaccine development, published papers, press reports, university reports and information published on social networks (Facebook, LinkedIn). I divided the sources into two categories, sponsors and researchers. The first category included the people working for the pharmaceutical companies or biotechnology organisations. The second category included the directors of the research sites responsible for the project's execution, through which I expected to get access to the site personnel like nurses, project managers and technicians. Unfortunately, in the SAVA case, there was a sub-register of the research site's principal investigators, therefore, in the field, I asked people involved in the case for the

information about the missed researchers and requested their support to contact them. This sub-register is explained by the complex structure of the SAVA case, as is discussed in Chapter 6, where the work of the site's principal researchers was under the umbrella of an SMO (Site Management Organisation).

One of the central decisions that a researcher must take is defining the study sites, the timeframe for the research and the boundaries of the study population (Schensul 2012, 81). I spent a short nine months between October 15<sup>th</sup>, 2014 and July 9<sup>th</sup>, 2015 conducting fieldwork. Over this period, I travelled to Colombia, Brazil and Mexico to conduct the interviews. Because I was familiar with one of the cases of study, KINGE in Colombia, I decided to initiate my fieldwork in this country and with this case. In Colombia, through a network of friends and family, the practicalities of setting my fieldwork were not difficult (finding somewhere to stay, transport etc.). However, in Brazil and Mexico, I also had to sort out these issues alone because it was my first time travelling to these countries. In Brazil, I spent most of the time in the city of Sao Paulo, and in Mexico in Mexico City. It was easy to arrange trips to assist at conferences and visit the research sites located in other cities by staying in these capital cities.

To convene the interview with the sources identified, I sent an email to the person with a brief leaflet containing information about myself, the objective, the length of the meeting, the topics of discussion and why the interview was relevant for my research (Appendix 3, has one example). The leaflet also explained the data handling and privacy closure, where it reassured every participant that they could withdraw from the interview at any time. In a few cases, I was requested to send questions in advance to the interviewee, to allow them to consider their participation in the research. If the person agreed to the interview, a date, time and place were convened. I must say, my nationality allowed me to get access to most of the cases. In each one of the three cases, at least one of the team members was a Colombian, so these researchers expressed their support for my research, and they were open to giving me an interview (I didn't know this in advance).

At the beginning of the interview, I explained to the participant more about the project and the objectives. I elaborated an informed consent form (ICF) in Spanish and Portuguese, and before the interview, I shared this one to participants before initiating

the data collection, and the interview started only after the person signed the ICF (Appendix 4.). The ICF stated that he/she voluntarily participated in the research, no reward was offered, they accepted the recording of the interview, and I stated that all information provided was confidential, so their identity would not be revealed. After the interview, I collected notes about observations and comments. Only one interviewee did not allow the recording of the conversation, then over the interview, I took notes, and once this one concluded, I made a voice note outlining the notes and the information that I remembered. Over the clinical trial, I reviewed the recordings to do an initial analysis and grasp the technical language of the practitioners of clinical research. In this way, my questions become more precise, and I could get a better answer. Also, the fact that I was trained as a biologist allowed me to talk with some researchers and sponsors using 'scientific' language, then complete information about the research was obtained. Additionally, at the time that I was conducting my fieldwork, relevant papers were published with the results of the researched cases, so this information was analysed to improve the quality of my interviews and examine the data previously collected.

Before travelling from Edinburgh to Medellín (Colombia), I coordinated an interview with the principal researcher of the KINGS research site and obtained authorisation to conduct interviews with the staff. He helped me to get access to the sponsor who was visiting the city. In this way, I started my fieldwork. Once I concluded the review of the first case, I continued my fieldwork in Colombia, getting data about the SAVA case in Bogotá. To my surprise, researchers contacted were directors of the SMOs and they did not execute the project. These SMOs coordinated the research sites, which were in rural areas across the country. To get access to these sites, I requested authorisation from the SMO's director. However, travelling to some of these sites represented a risk to me because sites were in territories with the presence of army groups (at that time, before the peace process). For this reason, I did not get authorisation from these researchers to visit and interview the personnel there, and, I considered these locations highly risky to travel alone. Nonetheless, I got access to other research sites located in the Andean zone, where the SMO's directors helped me to make a bridge with these researchers, so I travelled to these rural areas to research the implementation of the project in the field. Through SAVA's sponsor in Colombia, I got access to her peers in Brazil and Mexico.



Additionally, she introduced me to the regional director of the project, with whom I had an online interview, but I did not get explicit authorisation to use the information collected in the research. So, I did not include this interview in the study.

During my fieldwork in Colombia, I prepared the visit to Brazil, and I scheduled, through email, an interview with the principal researcher working on NUSTAN's project. This contact was the hook to travel to Brazil and initiate a snowball strategy to get access to other workers, especially in the NUSTAN case, where I interviewed most of the personnel directly involved in the project's execution. One element to point out was that I sent all my information in English because I assumed that researchers were familiar with this language. However, once I travelled to Brazil, I realised that not many people in the sites spoke English and they preferred to talk in Spanish or Portuguese. Although I'm not fluent in Portuguese, I took Portuguese classes in Edinburgh before my fieldwork, so this helped me to interact with people and paraphrase some expressions in this language. Then, in this country, interviews were conducted in English, Spanish and '*Portuñol*' (a mix between Spanish and Portuguese).

In Brazil, especially in SAVA's case, the access to the research sites was limited. In the first place, the sub-register of information about the principal researchers was large, so it was not possible to contact them directly. In the second place, SAVA's representative was highly reserved with his contacts and only provided me with information about one research site, working on a different project in Recife. SAVA's representative made clear that this was a personal favour because this researcher was his friend. Otherwise, he was not allowed to give me access to the other researchers. Although I interviewed this person, I did not include this data because it is not directly related to one of the cases. This situation placed a barrier to accessing the other sites; for this reason, information about SAVA sites in Brazil was not included in the analysis, which modifies the design initially proposed to understand the influence of the country level on the trial implementation, so most of the comparisons were between Colombia and Mexico. Nonetheless, to counteract this gap, I participated in local conventions to better understand the research context in Brazil. The other limitation was that I spent one month and two weeks in Brazil and this period coincided with religious and national celebrations. Then, this is a point that I need to consider in my next fieldwork.

In Mexico, I spent two and a half months researching the SAVA case, and I accessed the research site through two steps. At the interview with the sponsor, he accepted me to introduce me to the SMO director of the project in Mexico, which in turn (second step) also approved my visits to the research sites that he was coordinating in the country. Also, before my trip, I contacted other researchers associated with the project, so I scheduled interviews with them in Mexico City. I was strongly advised by the sponsor, researchers and personal friends in Mexico to avoid some states of the republic because of the internal conflict between drug cartels. For this reason, I visited three of the five sites because the other two were in violent areas. Once I got access to these locations, I coordinated the interviews, and I travelled to the rural research site, and there I collected the data.

One of the challenges was that people at intermediary levels felt that they did not have the right to talk about the research because the confidentiality that is involved in managing patients' data. However, when they understood that I was interested in their learning and working experience, establishing a fluent conversation was easy. In contrast, senior researchers were open to giving an interview and were much more open to answering the questions and sharing their experience; they knew their position in the project and did not see in me or the interview a threat to their work.

During data collection, I made reports on the progress of fieldwork. The reports were reflections about the pertinence of the concepts used in the interview schedule. For example, once I concluded the interviews about the KINGE case, I presented my first report. For this report, I transcribed the interviews using the software Express Scribe, and I analysed them using NVivo to verify the pertinence of the concepts and the model, and if the questioner was allowing me to collect the required information, this case worked as a pilot study. Based on this information I identified a third actor in the clinical trial that participated actively in the transfer of information, not only monitoring, the CRO, so I had to design a questionnaire that captured the role and participation of this organisation in this activity over the course of the clinical trial. Also, I identified that large part of the interview was oriented into the transfer process, so I had to adjust the interview to get more information about the use of knowledge. I discussed all this information with my supervisors via Skype.

The fact that I conducted most interviews in Spanish improved the quality of the interviews. Additionally, I collected secondary information like published papers and reports. Together, semi-structured interviews and documents allowed me to understand how, in each organisation, knowledge was employed to produce their project products and how these products were transferred across the firms.

### 3.4. Data Analysis

“Qualitative data analysis is essentially about detection, and the tasks of defining, categorising, theorising, explaining, exploring and mapping are fundamental to the analyst's role.” (Jane and Liz 2011, 5)

Determining the unit of analysis is important because it shapes the data collection and, specifically, the data analysis (Bhattacharjee 2012; Gerring 2004). In the literature of clinical trials and knowledge management in the outsourced or multi-organisational project, the unit of analysis is usually the firm. This perspective does not allow us to study the relevance of individual decisions directly and the acquisition, use and transfer of knowledge by people over the course of the project, either designing it or executing it. Because my thesis aims to study how, in multi-organisational projects, knowledge flows and is used to achieve the project goals, in this thesis the unit of analysis is the knowledge, data and information used, acquired and transferred by people over the course of the project. Because these units are intangible, those that can provide an account for this unit of analysis are the people working on the project. They are those that learn and know what and how to do the activities to achieve the objectives and solve the “productive enquiries” (Cook and Brown 1999).

To conduct the data analysis, I used a grounded theory ‘framework’ approach (Jane and Liz 2011). This method enables comparisons and associations between and within cases, being entirely suitable for the research design of this project, and it allows a systematic treatment of all units of analysis. According to Maggs-Rapport (2001), a framework approach ensures that qualitative studies are methodologically robust, and provides transparency about the analytical process employed. This framework considers five stages: familiarisation, identifying a thematic framework, indexing, charting, mapping and interpretation. Familiarisation with primary data took place through listening to

the records, transcribing them and reading the information once the transcription concluded. Also, I reviewed the local regulations and the published papers associated with each one of the cases. The next step was the identification of a thematic framework. This step was made using the model proposed in Chapter 2 in the conceptual model section. Data indexing was implemented using the software NVivo. In this case, I used the software as a reference manager, where I created a coding system based on the model designed to study the transformation of knowledge over the course of the trial and how the execution of the project progressed in each research site. Although I introduced the data in the software using the node tool that the programme has, I did not use the software analysis tools. To analyse my data, I codified each source in the nodes created according to the model proposed in the theoretical framework. It was easy to explore the data, compare it and identify trends using this software. Also, it was possible to conduct a data triangulation comparing responses between interviewees about the same topic. Notably, triangulation helped to contrast the narratives of the personnel involved in the same activities either because they shared functions executing a task in the same case (i.e. all the staff involved in training in the same case) or they had the same jobs in different cases (i.e. physicians' narratives in all cases). This analysis allowed me to determine the consistency of my data and to point out in those cases where discrepancies existed among the sources. At the end of this document at Appendix 2 is a table with a list of the interviews transcribed directly linked to the cases studied and the codes for the interviews quoted in this thesis.

Data were collected mostly in Spanish, which implied a translation process to produce the final document and quote the answers. Over the writing process, two problems emerged. The first one is that in Spanish there are grammatical and syntactical structures that do not exist in English, and the second one was that personnel employed local jargon to express ideas. To solve these issues, in the literature two approaches have been proposed. The first one is to translate the quotes into English once the rules of English structure are applied (Bassnett 2005, 32). However, this process can lead to the loss of information (Ervin and Bower 1952, 597; Rubin and Rubin 2012). The second approach consists of a literal translation, word by word, which can lead to the loss of meaning in English and the readability of the text. Therefore, to address this issue translating the information, I focused on achieving the same meaning of the expression,

doing a literal translation of the text. In those cases where syntactical issues emerged, I complemented the information within brackets, or footnotes, or in extreme cases, the quote was grammatically and syntactically corrected.

Some authors have argued that the extrapolation of results using cases of study can take place through an “analytic generalisation”, connecting the data with the theory (Mookherji and Lafond 2013). Therefore, the contribution of my findings to the study of multi-organisational projects will be through the discussion and comparison of the findings with the debates present in the literature. Some of these debates are the need for creating a shared knowledge across project members in different organisations, or the relevance of trust on the acquisition of knowledge, which is one of the findings in this research. In this way, I can compare, discuss and provide new evidence to the theoretical and conceptual debates that are around the flow and use of knowledge in multi-site or outsourced projects. I must admit that because of my previous background as a laboratory researcher, I do not pretend that the conclusions obtained in this thesis are entirely extendible to the entire universe of clinical trials or multi-organisational projects. For me, the results of any research are only valid for the context studied. Any generalisation requires new studies to verify if the new hypotheses are valid there. In the specific case of this research, for me, the execution of each multi-organisational project is unique in time, and nothing guarantees that, in a new project, the same people and same organisations would be working together and the results are replicated. In the cases studied, specific circumstances took place to bring together the organisations working on the project, circumstances that are not replicable in time. Secondly, human behaviour is not predictable and it changes as people obtain experience, even in the same project. Once the project concludes, the person and the organisations are not the same; they have gained or lost knowledge and probably would be facing a new project differently. Therefore, all generalisations should be cautious.

### 3.5. Ethical considerations

Before the beginning of data collection, I conducted the University of Edinburgh’s ethical self-audit Level 1 ethical review. The review showed that research design discussed here did not pose any cultural, physical or psychological risks to participants, in particular with the focus of the scheduled interview on aspects such as personal

interactions. Based on this evaluation, *I, Sara Valencia Cadavid, confirm that I have carried out the School of Ethics self-audit about my proposed research project: A model to study the flow and use of knowledge in Outsourced Knowledge Intensive Projects: A multi-case study of three vaccine clinical trials in Latin America. Countries researched: Colombia, Brazil and Mexico, and that no reasonable foreseeable ethical risks have been identified.*

To uphold the agreement between the participants and myself about data confidentiality, I took a series of steps over the fieldwork and afterwards. Over the fieldwork, some researchers and sponsors manifested that they wanted to be anonymous and they didn't want other persons associated with the trial know about the interview. Therefore, interviewing other people, I had to be cautious not to mention the other person's name or use explicit information that another source had provided, which could potentially expose that person. After each interview, I transferred the data on a password-protected computer, and I deleted files from the recorder, and for each file, I used a codification system, avoiding the use of personal names. Additionally, I created a table with the information of all records and I assigned a fictitious name and a code on the writing process.

### 3.6. Reflexivity

Through this project, I have been reflexive about my background and how it influenced my research. The study of the social world over the PhD was challenging because of my positivist views about the natural sciences before initiating my PhD. My undergrad is in biology, with an intense experience in laboratory work and statistics. My previous experience with the social world was related to voluntary activities, political activism and a consultancy project to conduct a diagnosis of the implementation of local policy in marginalised schools.

My reflections about the study of the social world before the PhD was low and, in fact, because of my training, I tended to use numbers and quantitative evidence that supported the arguments and dynamics of the spheres in which I was involved. This positivist position presented an initial conflict for me when I decided to conduct exploratory research to understand the flow of knowledge among research teams (an

initial proposal that changed as the project matured). Previous research on this topic has been qualitative, and the evidence shows that this process is dynamic and depends on the social relationships among actors, the people and the context in which interactions take place. This fact made me realise that although the social world is a reality out there (critical realism (Bhaskar 2008)), its study is challenging because multiple variables reshape the reality and what explains the dynamics in one social group does not elucidate the fluctuations in other social groups. Also, events occur in the real domain at times when the researcher cannot always be present, as is the case for this research. Therefore, in those cases where full observations are not possible, it is necessary to interpret the data collected to try to elucidate the reality. Then, the way to 'know' about the social world and the actions conducted by individuals or the people is through interpretative means, where the analysis of the acts is based on the understanding and interpretation of the meaning and purpose of the individuals studied and their actions (Bhattacharjee 2012). So, this new world about social research meant, for me, a turning point in the way in which I had conducted research, switching from quantitative research to qualitative research. Nonetheless, some of my previous experience contributed to the design of this research, as I can see now in this reflection.

From my background as a biologist, especially in cellular biology, and my previous experience doing quantitative research and standardising protocols and pre-clinical tests, it was evident to me when I worked in a laboratory that the results obtained from one experiment could not be extrapolated to other contexts and accounted for the same conditions. Then, interpretations of results had to be carefully made to explain a phenomenon, and any generalisation of results to a new context always required the statements of a new hypothesis and the execution of a new experiment to validate the previous results in the new environment. This perspective about the interpretation of results directly influenced the decisions that I made in my research design selecting three cases of study; three vaccines to prevent the same disease, and my precautions to generalise findings.

The fact that I was assuming a role as a social scientist when I was interviewing personnel at the research sites and from the pharmaceutical sector placed me in a new situation. Under this context, I was an outsider that wanted to know about their experience in clinical research. When I introduced myself as a student of science and

technology studies at the school of social and political science the responder assumed that I did not have a 'scientific' background, so he or she had to use simple and understandable language to explain the activities that they were conducting to me. However, as I employed technical language and I mentioned my background as a biologist, people changed their language and used more sophisticated jargon and the connection improved, so this fact improved the quality of the data gathered and its veracity.

### 3.7. Summary

In this chapter, I have summarised the critical steps that I undertook to design this project, collect the data and analyse it. In this chapter, I discussed the reasons why I selected a comparative case study rather than other approaches and how, using this method, I created strategies to achieve internal and external validity to produce data with high quality. In the reflective exercise that was writing this chapter, I presented the process and logic that I followed to select the three cases studied and the countries visited to collect data. In this chapter, I also discussed the data collection process, the selection of the method to collect data, the design of the tools to collect it and the implementation of the interviews in the field. Also, I presented the limitations that I faced over the data collection, like the sub-register of information, the language barrier in Brazil, the negligence of people to provide information about the project, and the presence of army groups or drug cartels in specific areas in Colombia and Mexico, which limited the access to those regions. Finally, in this chapter, I presented the process to analyse the data using a framework approach and the decisions made to present the data in English. Also, I discussed the ethical considerations associated with this project, managing the data and keeping sources confidential. Therefore, in this chapter, I summarised the main decisions, actions, and reflections that took place over the project's design and execution to ensure that this project was of high quality from a methodological point of view.



# Chapter 4: Use of internal and external knowledge by the sponsor to design the clinical trial

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## 4.1. Introduction

A clinical trial is a project where multiple actors participate. In these multi-organisational projects, each actor has its responsibility where the product of one organisation turns into the input of another project member. In the theoretical framework, the concept of interdependency was employed to define this dependence. In the pharmaceutical industry, the sponsor has the clinical responsibility for the project, being the one in charge of the design of the project and contracting actors such as the CROs or research sites. The outcome of the initial planning stage is the protocol. The protocol contains a description of the project's objectives, the scientific basis of the project, the procedures to produce the clinical and biological data, and the logistics of the study (Ottevanger et al. 2003). Nonetheless, the sponsor does not execute this protocol. Research sites and the CROs implement their respective tasks following the protocol. Then, because the protocol is the main knowledge product produced by the sponsor at the beginning of the clinical trial, the research question that emerges is: ***how did the sponsor acquire and use knowledge, data and information to design the clinical protocol?***

The implementation of a task requires the use of knowledge, information and data residing within the boundaries of the team and the acquisition of external knowledge. In the organisations, people use knowledge to refine data (M. H. Meyer and Zack 1996) or give a solution to problems (McElroy 1999). The present chapter precisely addresses the use of the knowledge residing within the boundaries of the team, and the acquisition of knowledge, to design the protocol. For this, I divided this chapter into two sections. The first section discusses the relevance of the previous experience and previous results to produce the protocol. The second section addresses the acquisition of external knowledge to design the clinical protocol, discussing the direct

communication between source and receptor, the permeability of teams to external knowledge, data and information and the use of boundary spanners (Tushman 1977) to access external data. The last section presents the conclusions of this chapter, where I show how clinical teams transform their knowledge, data and information in the protocol.

## 4.2. Management of knowledge and information residing within the boundaries of the clinical team to design the protocol

The clinical protocol has the step-by-step of the project, and it has all the scientific basis of the project. However, the knowledge employed by clinical teams to create the protocol remains relatively understudied. Previous research on protocol creation has focused on the interaction of people writing the protocol and the physical writing protocol process (Eapen 2007; Gennari et al. 2004; Weng et al. 2004; Weng et al. 2007). Nonetheless, they have not addressed the conceptual and practical knowledge involved in the protocol creation and how it is used to create the protocol. Aspects that this section discusses.

During my interviews with clinical trial coordinators at KINGE, NUSTAN, and SAVA I asked what knowledge, information, or data they employed to design the clinical trial protocol. Personnel at these firms included in their answers five elements that shaped and constituted the initial knowledge, data and information required by the clinical team to design the protocol (Table 3). They are; (1) the knowledge and experience of the clinical team; (2) the previous results of preclinical and clinical phases; (3) the guidelines designed by the WHO to evaluate the vaccine and implement laboratory tests to measure antibodies in humans (two different guidelines); (4) the sponsor's commercial interest and operative and social information and (5) epidemiological data about the disease incidence and prevalence in the locations when the trial took place.

Like Table 3 shows, only three of the five elements were available within the firm in all three cases and the other information and knowledge resided in external organisations (sources), therefore, the clinical teams had to find strategies to access these sources. These elements coincide with the conceptual knowledge described by Gennari et al. (2004) in an ethnographic study about the protocol writing process. Nonetheless, their

research focused on the management of multiple versions to write a single protocol, and not on the use of different knowledge and information sources to design the trial.

In this section, I will address the relevance of the knowledge residing within SAVA and KINGE clinical teams (Element 1) and previous results (Element 2) to adapt the WHO guidelines (Element 3) to design the clinical protocol. In the NUSTAN case, I will discuss how the team accessed previous results and used related knowledge to design the protocol.

**Table 3. Initial knowledge, data and information employed by clinical teams to create the clinical protocol.**

Knowledge, data and information	Location of the source		
	SAVA	KINGE	NUSTAN
<b>Element 1.</b> The knowledge and experience of the clinical team.	Internal	Internal	<i>External/ Internal</i>
<b>Element 2.</b> The previous results of preclinical and clinical phases.	Internal	Internal	<i>External/ Internal</i>
<b>Element 3.</b> The guidelines designed by the WHO to evaluate the vaccine and implement laboratory tests to measure antibodies in humans (two different guidelines).	External	External	External
<b>Element 4.</b> Sponsor's commercial interest.	Internal	Internal	Internal
<b>Element 5.</b> Operative and social information and epidemiological data about the disease incidence and prevalence in the locations when the trial took place.	External	External	External

#### 4.2.1. The experience of the clinical team as a base to create the protocol and the use of previous clinical and pre-clinical results

Previous studies have revealed that protocol creation is a cooperative scientific process within a group of interdisciplinary clinical trial experts (Weng et al. 2004). In the three

cases studied, the clinical teams responsible for the protocol design comprised of disease experts, clinical writers, statisticians and epidemiologists. These clinical teams were responsible for writing the protocol defining the study intervention, study design, participants' eligibility criteria, response variable, sample size, patient management procedures, monitoring for safety and benefit, and data analysis approaches as indicated in papers published with trial results. Clinical team members reported how the professional background of each one of these experts contributed to the design of the project "because to write a protocol it needs a deep knowledge about the pathology, the statistics, and many other things" [PM-USP, NUSTA, April-01-2015]. Then, each one of these members contributed from its area of expertise to the protocol writing. This element supports the argument of Tseng (2004), which considered that specialist knowledge of members of multi-functional teams is necessary to address the complexities that emerge in the projects.

In the case of NUSTAN new clinical teams had to be configured, in contrast, the stability of KINGE and SAVA's clinical team members between project phases allowed that the practical knowledge and experience acquired on previous trials (Element 1 Table 3) benefited the protocol writing. A review of papers published by SAVA evidences how the team members were constant (Sabchareon et al. 2012; L. Á. Villar et al. 2013; L. Villar et al. 2014a). In this case, ten team members participating in the Phase II trial contributed to the design of the Phase III trial. In the case of KINGE, also the accumulated experience and knowledge of the clinical team was fundamental to design their Phase II, where the firm designed all the protocol, as Dr Jaime Plata (KINGE Sponsor) pointed out in the interview: "*the principal study (Phase I) was designed by the company, the same for study Phase II*". For him, writing a protocol seemed an easy task that is part of his regular academic work. However, in this case, between Phase I (2011) and Phase II (2012) KINGE merged with Singaporean biotech. As a result, new members arrived at the team contributing with their insights to the design of the clinical trial Phase II and its implementation, as Dr Plata explained in the interview. For example, the Singaporean company used to outsource the project to a CRO, then in the new Phase II the project was outsourced and the contacts and management were through the Singaporean members. Therefore, new people in the clinical teams were sources of new knowledge and new practices to implement the project. Nonetheless, the fact that

KINGE personnel continued participating in the other phase of the project allowed that the knowledge acquired in previous phases was conserved and used in the Phase II trial.

Members of NUSTAN, KINGE and SAVA employed previous clinical and pre-clinical studies in the protocol design (Element 2, Table 3). In the SAVA case, a paper published in 2010 summarised the results of all pre-clinical and clinical trials implemented up to that date (Guy, Saville, and Lang 2010). This paper indicated how previous clinical and pre-clinical results were used to design the new clinical phases to test the vaccine's security and its immune performance. This publication revealed how the team started their clinical evaluations with a single dose of the vaccine and the last trial was implemented using a three-dosage schedule to induce a satisfactory immune activity (seroconversion) in the volunteers. The fact that the vaccine did not show a high efficiency with a single dose required intermediary trials to determine the optimal combination of vaccine schedules, dosage and administration route to be used in Phase III. KINGE used the results of the Phase I to narrow the scope of Phase II. In Phase I, KINGE compared two dose levels and two different administration routes (subcutaneous (SC) or intradermal (ID)) to identify the best dosage-route combination to stimulate the immune system. The clinical team using these results designed a Phase II trial evaluating a subcutaneous administration route, the high dosage formulation and two dosage schemes (day 0 and 91). Then, based on previous results, teams modified the hypothesis and variables evaluated in the new trials.

In the literature about project teams, the relevance of team stability for the project success (Savelsbergh, Poell, and van der Heijden 2015) has been discussed. Stable teams enable learning and intra-team coordination (Akgün and Lynn 2002) and also facilitate coordination of interdependent work (Edmondson, Dillon, and Roloff 2007). What the cases of KINGE and SAVA indicate is that personnel stability allows using the experience obtained from the previous project to the new trial. However, the arrival of new personnel also brings new approaches to design a project, such as the KINGE case indicates. The evidence presented for KINGE and SAVA supports the argument that knowledge is re-used between interrelated projects like clinical phases (Owen and Burstein 2006), where the access to the knowledge acquired previously is critical for its further use in related projects (Formentini and Romano 2011). Therefore, in the clinical trials, the knowledge accumulated over the course of previous phases becomes the basis

for designing the protocol, and the continuity of the personnel across phases (interdependent-projects) allows the inclusion of these experiences in the design of the new protocol. Consequently, organisations sponsoring clinical trials should create a mechanism to ensure the continuity of their personnel in the organisation, so the knowledge acquired as a result of the trial stays in the boundary of the firm and can be employed in future projects because this knowledge is the base for creating the new projects.

Table 3 indicated how, in the case of NUSTAN, the knowledge and experience of the clinical team (Element 1) and the previous results of pre-clinical and clinical phases (Element 2) had a dual origin. In the case of NUSTAN, it was necessary to configure a new clinical team hiring new personnel and consult with external organisations on the results of previous clinical trials to design the protocol. The fact that NUSTAN did not participate in preceding clinical phases and the organisation did not have a clinical division to conduct clinical trials explains these differences. Therefore, NUSTAN had to create a new clinical team to design and execute Phase II to evaluate the vaccine differing to SAVA and KINGE cases.

Below, I will address this specific case, and the lessons to learn from the NUSTAN experience for those cases where sponsoring organisations do not have previous experience conducting clinical trials to evaluate new products.<sup>10</sup> This reflection is relevant in the context of Latin America because if many national pharmaceutical companies and research institutions such as NUSTAN are developing new products or acquiring licences for new ones<sup>11</sup> to implement clinical trials, then NUSTAN's experience can contribute to these cases.

In 2009, the NIH decided to implement a non-exclusivity licence mechanism for its new vaccine. The NIH licensed the vaccine to five organisations, including NUSTAN in Brazil, to continue the vaccine development, especially the clinical Phases II and III,

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<sup>10</sup> I make emphasis on evaluating new products, because there is another branch on clinical trials that evaluates new formulations or combination of drugs which have a different mechanism to be evaluated than new drugs.

<sup>11</sup> Information that is the result of a parallel research that I conducted to identify models to develop new products in Colombia, Brazil and Argentina.

and create the infrastructure to produce the vaccine locally. Up to that date, the NIH had implemented all pre-clinical and multiple Phase I trials to identify the best vaccine formulation.<sup>12</sup> NUSTAN implemented the clinical trial Phase II in 2013, and Phase III initiated in 2016. Nonetheless, between 2009 and 2013, NUSTAN had to create a series of capabilities to implement the trial, including the configuration of the Division of Clinical Trials and Pharmacovigilance at the institute to design and coordinate the project. To create the clinical division, the institute's director hired personnel with experience conducting non-interventional clinical projects, as Dr Pablo Esmeralda explained:

“The strategy employed by NUSTAN was to search for personnel that maybe did not have that experience in the industry, but in some way had previous experience doing clinical trials in one or other way. They said we are going to assume this challenge together. And this is how I ended up on this journey. Then, a small group of people was gathered to try to make that development.” [NUSTAN Chair, Apr-13-2017, underline added]

Although NUSTAN recruited people with previous experience, according to Dr Pablo Esmeralda (NUSTAN Clinical R&D Manager), the configuration of the clinical team was challenging because “it is quite difficult to find outside the USA and Japan people with the knowledge to make protocols and generate a clinical development plan”. Then, this quote illustrates how scarce and centralised the knowledge is to lead the development of a product clinically. This knowledge is within the boundaries of the pharmaceutical industry in countries like USA, Japan and some countries in Western Europe with a strong background in implementing industrial clinical trials, as was presented in the introduction of this chapter. However, in countries where there is not a robust pharmaceutical industry, the knowledge to be a sponsor, to lead clinical projects and to create the protocols is scarce. People that had worked in academia or as a consultant for the WHO or the PAHO are those that possess related knowledge, and are those at the end who lead clinical trials like the one conducted by NUSTAN. Therefore, in the context of Latin America, it is important to create strategies to strengthen the knowledge to design and implement clinical trials of new products, which differs from clinical trials of commercial products.

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<sup>12</sup> This process consisted of identifying in each virus which concentration was the best to induce the highest immune answer.

As I presented in Chapter 2, the acquisition of knowledge is neither direct nor straightforward. It demands a learning effort (Akbar 2003) that employs the conceptual knowledge possessed by individuals. However, when this knowledge is not available within the team or organisation, one option is to introduce knowledge hiring people, a second option is training employees, and another option is creating alliances and partnership with external organisations to access to resources that cannot be recreated internally (Powell, Koput, and Smith-doerr 1996). These activities were necessary to acquire knowledge for the NUSTAN clinical team. The fact that NUSTAN selected personnel with related knowledge defined the bases from where the clinical team could build its knowledge of how to be a sponsor, design a clinical trial project and implement the clinical trial. The process to create the team's knowledge to be a sponsor is illustrated in the following quote:

“So, we started to design a structure of what is being a clinical trial sponsor. So, inside that structure we began to think, how is a product developed? This knowledge is part of the core business of any pharmaceutical company. When do you have a product, how do you develop it? So, we started to study and work on that... The clinical development has been an internal exercise, regarding what the disease immunology is, what neutralising antibodies are, and based on that we started to question the mathematical models that were published and we began to create our understanding.” [NUSTAN Chair, Apr-13-2017]

This statement nicely captures different elements of the learning curve of the team. In the first place, it illustrates how learning took place within the boundaries of the team, and a series of questions guided this learning. Secondly from the expression “we started to study and work on that” it can be inferred that the team had to acquire information, analyse it, put it into practice, and discuss it to create their knowledge about how to design a protocol. This process coincides with what McElroy (1999) proposes in his model, where problems are evaluated and based on this analysis; if the knowledge possessed is not enough to solve the task, the acquisition of knowledge is triggered. All this process to generate new knowledge as a team was guided by a cycle of questions and answers that strengthened their knowledge as sponsor and, at the end, defined what acquired information and knowledge was useful and valid to create the clinical trial.

In this case the clinical team had to consult external sources to recreate in the firm's boundary knowledge obtained in previous clinical trials. The primary source of external



knowledge to learn how to design the protocol was Dr Anna Battilega (pseudonym). She was the person responsible at the Johns Hopkins Bloomberg School of Public Health for implementing clinical trials Phase I for NUSTAN's vaccine. The NUSTAN team regularly contacted her to obtain advice on the protocol design and obtain information about the previous trials that they implemented. In this way, through a direct communication channel with an external source, the team accessed external information about previous trials and knowledge to design the clinical trial Phase II. As a result, the protocol developed by NUSTAN aimed to evaluate the same vaccine concentrations employed by the NIH (source, clinical trial protocols and NUSTAN Presentation) using two dosages administered subcutaneously to a population between 18 and 59 years old.

In summary, the NUSTAN case illustrates the process to develop new knowledge to design a protocol in a case where clinical teams do not have previous experience with the research product and designing clinical trials. In the first place, it is important to hire personnel with knowledge close to the work to be undertaken, then from this knowledge-base, it is possible to build the new knowledge. Second, in the case that the project to implement is interdependent with a previous project, the team should ensure a communication channel with personnel involved in earlier stages to get access to knowledge previously developed and use it in the new project. Thirdly, the creation of the new knowledge requires a learning effort, where discussion and reflections are part of the activities to learn and create the necessary knowledge.

#### 4.2.2. Use of guidelines to design the protocol

Within the clinical trial community, since 1983, statistical guidelines to design clinical protocol (Altman et al. 1983) and address knowledge gaps such as the statistical knowledge of the clinical teams which is reported as missed in the clinical teams (Romano and Gambale 2013; Wyatt et al. 1994) have been proposed. More recently, researchers and the WHO have created guidelines to address the evaluation of products for specific disease, providing medical and statistical knowledge to protocol designers (Lorch, O'Kane, and Taubel 2014). In the cases studied, sponsors' personnel indicated that they used published guidelines as starting points to design their respective protocol for the vaccines evaluated (Element 3, Table 3). The guidelines employed were

the ones created by the WHO. The Department of Immunization, Vaccines, and Biologicals at the WHO developed two guidelines with the objective of resolving technical doubts about the design of the clinical protocol for the vaccine candidates. The public for these guidelines were national health authorities – who evaluate the protocol – and research scientists – who design the protocol to assess the vaccine. The first guideline was the 2007 WHO guideline “for plaque reduction neutralisation testing (PRNT) of human antibodies to the virus”<sup>13</sup>. And the second one is to design *the clinical evaluation* of vaccine candidates in endemic areas (Phase I- IV) (Initiative for Vaccine Research WHO 2008).

The first guideline was employed by the three clinical teams on the design of their trials, as is stated in their published papers<sup>14</sup> and Dr Pablo Esmeralda (NUSTAN Clinical R&D Manager) said, “there exists a kind of standard protocol developed by the WHO that everybody has to follow, ... it is a protocol well established because the answer is simple, there are so many things to answer”. Ana Diamante (SAVA-Col) reinforced this statement by saying that “the WHO and the PAHO<sup>15</sup> have guidelines to design clinical trials for infectious diseases, so you have to rely on these (guidelines)”. Also, the SAVA coordinator in Mexico explained this: “There is a lot of literature, and the protocol is made based on the previous protocol of disease burden to define which efficacy it [the vaccine] should have.” [SAVA Sponsor Mex, May-07-2015] Personnel at the clinical teams expressed how they employed clinical trial templates and these guidelines based on their aims. The next quote provides a clear example:

“There is a statistical objective to prove that the vaccine is safe. [The design] depends on the type of population that you want for the study, the ages, the area background [epidemiological information] per country, all this affects the design.” [PI- R-IDVI, KINGE, Oct-15-2014]

Like the quote indicates, the team had to consider multiple variables in the design, considering the population, the research product and the disease epidemiology. The process to adopt the guidelines to the research product and context required an

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<sup>13</sup> This biological measure correlates best with protection from subsequent virus infection. The objective of this document was to harmonise the measure of levels of Flavivirus-neutralising antibody titers in the serum of vaccinated, or infection-immune individuals.

<sup>14</sup> See paper (Guy, Saville, and Lang 2010).

<sup>15</sup> Pan-American health organisation.

analytical process and the use of information collected in previous trials. If the team did not have information to proceed with the design, they had to access to external sources to acquire knowledge or information to continue the process (the next section will detail this acquisition process).

Nonetheless, not all sponsors developing vaccine candidates accepted these guidelines. The NUSTAN team strongly criticised the WHO guideline for plaque reduction neutralisation testing (PRNT) as the following quote illustrates:

“The WHO have some guidelines of how should be [executed] the PRNT, but when you start to see in detail those guidelines, many holes were never closed like: how should the PRNT be implemented? For example, PRNT against what? Against the wild virus or the vaccine virus? Should there be a reference virus? How is made an inter-laboratory validation? What is the PRNT that I should use, PRNT 50, PRNT 90? How should be done the specificity test? Is it worth? Nothing of that is resolved [in the guideline]. The guideline exists, and all papers [trials conducted by other sponsors] refer to that guideline, but in practice, many technical details about how to do it never were resolved, so each producer is doing it, in the way they consider [appropriate].” [NUSTAN Chair, Apr-13-2017]

According to the NUSTAN Chair, the guideline had technical holes that any actor involved in the vaccine context addressed. In his view, the content of this guideline was designed to favour the evaluation and introduction of the first vaccine candidate available, which was the SAVA’s vaccine. Then, there was a conflict of interests. According to him, in the guideline the WHO did not include technical aspects needed for the evaluation of other vaccine candidates. The fact that the other vaccine candidates used different biological models<sup>16</sup> could have affected the way to evaluate the PRNT. As a result, they decide to use the PRNT protocol developed by the NIH and some of the WHO recommendations. The NIH had implemented previous clinical phases, then, adopting NIH protocols, NUSTAN could make inter-laboratory validation to compare results among trials. Therefore, this analytical process gave place not only to the protocol. This analysis leads to criticisms of the scientific bases of the guidelines and to the adoption of alternatives to close the gap.

As NUSTAN case illustrates, and the quote on page 72 shows, as the clinical team get confidence in their knowledge, they can criticise or call into question other teams’

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<sup>16</sup> They were not using yellow fever virus; instead, they used recombined versions of virus trips.

approaches and the published literature, as it was in the case of the use of guidelines to design the protocol, which is part of the learning process of a new team. In this case, the team defined what was in the guidelines that answered the scientific criteria of their project design. So as this case shows, once a certain level of dominance of a topic has been achieved, it is possible to engage in the discussions taking place in the academic community. Then, this case provides evidence of how clinical teams continually evaluate the information acquired to design the project and the protocol, as McElroy (1999) suggests, on the creation of knowledge products, and this evaluation includes the raising of critiques to the knowledge accepted in a community. Therefore, the use of guidelines is not a straightforward process to create the protocol; it is an activity that demands reflection, criticism and comparisons of the guidelines with the knowledge of the clinical team.

#### 4.2.3. The influence of the commercial interest of the sponsor on the project design

The commercial interest of each sponsor determined the design of the clinical trial and the protocol regarding the population included, the sample size and if the clinical trial would be multinational or in a single country (Element 4, Table 3). KINGE and NUSTAN Phase II had similar objectives; to evaluate the vaccine immunogenicity in healthy subjects.<sup>17</sup> In both projects, the number of volunteers to enrol was similar: KINGE enrolled a total of 360 participants and NUSTAN 300 participants. However, KINGE and NUSTAN had different commercial interests. KINGE was interested in introducing its vaccine in Latin America and Asia-Pacific countries,<sup>18</sup> and NUSTAN only in Brazil. This difference meant that KINGE implemented a multi-national clinical trial in four countries compared with NUSTAN, which only included Brazil. Because of this, KINGE had to collect epidemiological information from each one of the countries, even if they had just one site there. A multi-national project involved having a monitoring team in each country, then this influenced the selection of the CRO. In the case of KINGE, this multi-national design implied an additional effort because they had to be

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<sup>17</sup>All objectives were to evaluate the safety, tolerability and immunogenicity of the vaccine, the incidence of vaccine virus replication, and the immune response induced by the vaccine in populations with previous exposure to the virus.

<sup>18</sup> In some countries, the registration and licensing of clinical products (vaccines, medical molecules) is favoured if part of the data of the clinical trials was obtained in that country, with the local population.

sure that the protocol fulfilled the regulations of each country included. In contrast, NUSTAN only had to implement its trials in Brazil because they “are doing this project for the Brazilian population”, as NUSTAN’s Chair said. Because Sao Paulo was in the middle of an epidemiological peak, they decided to implement the trial in two research sites located at the University of Sao Paulo. Therefore, the planning process, the acquisition of epidemiological data, and the monitoring was more straightforward than in KINGE. Then, the interest of implementing a multi-national trial demands extra efforts on the project planning, including initial data collection.

Another example of the implications of the commercial interest of the sponsor on the project design is evident in the SAVA case. In this case, initially, the clinical team did not consider implementing the trial in Brazil because the company did not have “a sort of department of clinical trials in Brazil” [SAVA Sponsor Brz, April-10-2015]. However, in Brazil, the virus is highly endemic, and Brazil is the biggest market of all Latin America for a potential vaccine. Also, for the sponsor, implementing a clinical trial in Brazil enables the obtaining of the registry to commercialise the product. Using these arguments, personnel in Brazil working in one of the pharmaceutical holding firms proposed to include Brazil in the trial, as Wallace Coutinho, coordinator of the project, said:

“The country is the most important in terms of the market in Latin America; we are the 7<sup>th</sup> or 6<sup>th</sup> today in the pharmaceutical market... in the end, we were invited as a country to participate because sort of pressure from the market, so it doesn’t make sense if Brazil doesn’t take part of the trial because we will offer a massive market in the future at the end.” [SAVA Sponsor Brz, April-10-2015]

So, SAVA included Brazil in the project because of this market pressure, and to coordinate the project, SAVA created an alliance with the pharma division of the group to outsource the project to the clinical unit of the pharma division to coordinate the trial locally. This team had to learn how to implement a vaccine trial based on their pharma experiences. Nonetheless, this learning was reported as challenging because endpoints evaluated in a pharma trial differ to the endpoints adopted in vaccine trials. In a pharma trial, endpoints include reaching a certain number of deaths or monitoring surrogate variables associated with health improvements. In a vaccine trial, the number of diseases reported defines the trial endpoint. Therefore, operative teams in Brazil had to develop new knowledge about how to implement a vaccine trial, as SAVA’s clinical

trial coordinator in Brazil indicated. In conclusion, the market interest of the sponsor to sell its vaccine directly influenced the design of the clinical trial regarding the number of volunteers to be recruited and the countries included.

### 4.3. Acquisition of external knowledge, information and data

The knowledge of the clinical team and the accumulated data and information produced in the clinical trials are fundamental blocks to design a clinical trial. Nonetheless, in the three cases studied, the clinical team had to acquire external knowledge, information and data to design a clinical protocol (Element 5, Table 3). The way of accessing this information, knowledge and data varied between cases. In the case of SAVA, it was necessary to use boundary spanners. In contrast, in the cases of NUSTAN and KINGE, researchers had direct contact with the source. Also, over the designing phase, the clinical team received suggestions on designing the project from external sources, like the national regulatory agencies and clinical researchers which, in some cases, were accepted but not in others. In this section, I continue tracking down the knowledge flow to design the protocol. I will specifically discuss the acquisition of external knowledge and information by the clinical teams, paying particular attention to the channels employed to access to these sources (direct communication or the use of intermediaries) and the permeability of the clinical team towards external information that was and was not directly requested by the team.

#### 4.3.1. Accessing and introducing knowledge, information and data required by the team

Table 3 indicated how clinical teams required epidemiological information to design the trials, and they had to know logistical aspects about the countries and locations selected to anticipate any adverse situation and adapt the protocol to the local requirements. SAVA and KINGE clinical teams were in the USA, and the trials were in Latin America countries. Because of this separation, clinical teams did not know the practicalities to implement the protocol in these countries. Therefore, clinical teams acquired this information from local sources, creating inter-branch communication channels or inter-organisational channels. In the case of SAVA, the company had branches in Mexico, Colombia and Brazil, so the clinical team consulted the

information required to the local branches – inter-branches channel – as the next quote indicates:

“We [branch] have an input... because we are going to do the studies in Mexico, we see if Mexican regulatory times does not impact the project, the project has to consider vaccination campaigns, that we don’t have any problem with the sites. Then, our input is relevant.” [SAVA Sponsor Mex, May-07-2015]

In the KINGE case, the principal researcher had direct contact with the research group because they have a long story of scientific cooperation, then a direct communication channel between the two organisations allowed them to consult information directly (inter-organisational channel). One example of this communication is the next quote:

“We had a meeting face to face (with the site personnel) ... I had to understand the regional dynamics, because many times, I believed that something that I do in the United States they (R-IDTV Colombia) do it in the same way. Nonetheless, they tell us, no, here that cannot be made, or that is not correct you must change it. So, I had to make changes based on that.” [Sponsor- KINGE, Oct-25-2014]

For the inter-branch and inter-organisational channel, both quotes show how a direct communication between the research sites and the source allowed to clinical team members to obtain rich insights into the local context. Insights obtained from local branches and sites allowed them to define the inclusion of research locations to the project. For example, Dr Jaime Plata [KINGE owner] has been interested in working in Apartadó-Colombia because this municipality presents a high disease incidence, which is ideal for running an efficacy clinical trial in less time. However, the region lacks adequate transport connections to send the biological samples from the site to the USA in less than 24 hours, so for this reason, the location was not selected. In KINGE and SAVA cases, sponsor personnel manifested the need to know in advance in which places it would be possible to implement the project, especially for security conditions: “you know that in our environment, it is not easy to work because of the insecurity” [Sponsor- KINGE, Oct-25-2014]. Unfortunately, in Mexico and Colombia, the drug traffic and internal conflict limited the implementation of the trial in highly endemic areas. For example, in Mexico “there were areas where the incidence was high, there was the population, but not the security conditions” [PI 1-Site2, SMO-3, SAVA-Mex, May-15-2015]. The exclusion of endemic areas in a clinical trial has consequences on the project results because without this information it is not possible to infer the vaccine’s efficacy in specific epidemiological scenarios where different combinations of the virus

circulate. Nonetheless, the security of people working on the project is essential, and despite the relevance of data, they cannot be exposed to these risks.

The evidence for KINGE and SAVA's cases indicate that the teams were receptive and used the insight gained from the local branches (SAVA) and local researchers (KINGE) to adapt the protocol to the local contingencies modifying procedures or coordinating the implementation of the clinical trial. Also based on this evidence, it is possible to say that in these two cases, the clinical team was permeable to this information because the headquarters demanded the information and they needed to understand the local conditions to determine the feasibility of the trial in the country, which is vital to coordinate the implementation of the project in multiple countries. So, the direct demand for information from the clinical team makes them highly permeable towards external sources.

Only NUSTAN requested from external sources knowledge or information directly associated with the scientific content of the clinical trial, and they were open to receiving knowledge from sources that they considered valid. In this case, NUSTAN's clinical team established collaborations with the principal researcher, Dr João Eduardo Espinela, considered an expert in the field of immunology in Brazil, to design the protocol and find alternatives to the methods employed to evaluate the immunology of the vaccine, as the following statements capture:

"The first draft was made by colleagues at NUSTAN, so they sent me the draft, and I was able to contribute to the study design and how the protocol was written." [PI-USP, NUSTAN, Apr-01-2015]

"On the study Phase, II João is helping us a lot. Now that the theory of neutralising antibodies is in check [he is] helping us to find something on cellular immunology that can turn out to be another type of protection marker." [NUSTAN Chair, Apr-13-2017]

These quotes indicate NUSTAN's intention to receive comments from the principal investigator and co-create new knowledge to solve a knowledge gap present in the scientific community. These quotes also demonstrate the high permeability of the team to the external knowledge when they requested it and consider that the contra part has a valid knowledge that is trustful and useful for the project.



The fact that the NUSTAN team was new and they had to acquire more scientific knowledge than the other two cases to design the project can be one factor that explains why NUSTAN shared the protocol with local researchers. However, I consider that behind the openness of NUSTAN researchers to co-create the protocol with other researchers, is the fact that NUSTAN wanted to propose an alternative model for the way in which clinical trials are designed and conducted in the pharmaceutical industry. According to the NUSTAN Chair in the industry, clinical trials are poorly exposed to the scientific debate. In their case, they wanted to discuss, with researchers and the community, the protocol to make it more inclusive and scientifically robust.

There are cases in which the sources in the country do not have the information or data required by the clinical team to design or adapt the protocol. Therefore, local teams had to design strategies to access data and information. For example, SAVA required epidemiological data of the countries included in the project to understand the disease distribution in each country over the last five years before the study. Clinical teams needed this data to calculate trial power and vaccine efficacy, as stated in SAVAs' Phase III paper:

“In these calculations, we assumed a dropout rate of 20% and a disease incidence of 0.64%. The assumed incidence was based on mean [disease name] incidence rates in the 4 or 5 years before enrolment, according to passive surveillance data provided by the municipalities in which the trial was conducted.” (L. Villar et al. 2014a)

To obtain this data and define the number of people to enrol per site, local branches acquired the role of boundary spanners, facilitating the transfer of data between the clinical team and the ministry of health, as SAVA's project manager in Colombia indicated:

“When you are designing a clinical trial you have local experts, we are those managing the trials locally, and WE help to search information... Those that design the studies are very centralised, and they don't have all information, so the first thing that they have to do is to contact local people in those places... You need to surround yourself with public affairs teams; they will make all negotiations with the public entities<sup>19</sup>; they will help you to get all data from the government that you need for the study.” [SAVA-Sponsor Col, Mar-24-2015, underline added]

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<sup>19</sup> At the national level, health ministries have surveillance systems for some diseases to identify the incidence, the locations, the serotypes circulating, the age of infected people, etc.

Therefore, as it is possible to infer from the quote, the public affairs in endemic countries were responsible for searching and accessing the data and information on external sources to then introduce it in the organisation and transfer it across teams. In this case, the public affairs team refined these databases to select only the information and data requested by the clinical teams, because the “countries do not provide the databases as you need it” [SAVA-Sponsor Col, Mar-24-2015]. After this process, branches sent the data to the clinical team. The clinical team using this data calculated the *trial power*<sup>20</sup> for the entire trial and each country (Colombia, Honduras, Mexico, Brazil and Puerto Rico). Also, with this data, they identified possible locations to implement the protocol and made the respective analysis to define the sample size. So, teams employed this information in the project design. Nonetheless, it is relevant to consider that the final selection of sites depended not only on the data analysis. The availability of technical capabilities in each country to implement the trial and create alliances with public and private SMOs (Site Management Organisations) were factors that defined the sites, the number of locations and the number of volunteers in each site, as was presented above.

Knowledge management scholars have argued that organisations need to take care of their ability to manage challenges across boundaries (Levina and Vaast 2014). Boundary spanners emerge as a solution to these challenges. These are individuals who enable the sharing of knowledge by linking groups separated by location, hierarchy or function (Ansett 2005; S. Gupta and Polonsky 2014; Levina and Vaast 2014; Alavi and Leidner 2001). Levina and Vaast (2014) propose the presence of two boundary spanners, nominated boundary spanners and boundary spanners-in-practice. The first ones are officially designated with specific responsibilities, whereas the second ones become spanners as a result of their actions and not necessarily because someone designated them with such a role. The SAVA case illustrates how headquarters nominate local branches as boundary spanners responsible to search for data. Moreover, these boundary spanners must use their knowledge about the requirements of the clinical teams to refine the data based on these needs and transfer it to the clinical teams. Then, in the SAVA case, boundary spanners are not only mobile actors who carry data, but

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<sup>20</sup> The trial power is the participants' sample size calculated to minimise random errors; this depends on the desired age group and defined end-point. A study needs sufficient power to conclude about the effect of a treatment (Wang and Bakhai 2006, 9).

they are also active actors who interact with the data, processing them before being sent. The clinical teams employed in the protocol design the data and information accessed by these boundary spanners. Therefore, it is possible to say that a team is permeable to these external data and information in those cases that the organisation nominates its boundary spanners and assigns specific responsibilities directly related to knowledge acquisition.

#### 4.3.2. Selective permeability to external knowledge and information not requested by teams

Up to this point, I have discussed how clinical teams accessed to external information that they demanded to design the protocol and the use of their previous experience and results to design the protocol. However, clinical teams also receive information and knowledge not directly requested, that they might have or might have not considered in the design. Therefore, here I will discuss how teams manage this unexpected knowledge and how the permeability of the clinical team mediated the use, or not, of this external knowledge.

Initial drafts of the protocol in rare cases are shared with researchers to get feedback. In the clinical trial industry, the traditional practice is that the clinical team shares consolidated versions of the protocol with researchers only when the team is configuring the research network, as the next quote evidences:

“The company always decides what study it wants to do and then searches for a principal researcher and says this is what we need to do, it is the company decision. Of course, over this process, there is some communication with the principal researcher to make small modifications, but the principal study is designed by the company.” [Sponsor- KINGE, Oct-25-2014]

Then, as this quote suggests, the clinical team does not expect substantial comments on the project design from researchers. The section 4.3.1 presented how the sponsor is interested in discussing only information associated with the local regulation on procedures to implement the project. But the discussions that take place among the two parts are not associated with the core methodological design of the project, excepting the NUSTAN case. So, the clinical team does not have a clear intention to receive external comments because these are not expected or demanded. However, in the SAVA case, one atypical situation took place. One of the local researchers, Dr Rubi,

considered that the protocol had some designing problems and, therefore, he suggested amendments, as he explained:

“I did corrections to the protocol that were not introduced because the laboratory didn’t want... [immunological explanation about his suggestions] ...So, what they accepted to modify was that they would take a blood sample on the first five days to review if the person was positive [to the virus]. That would help us to know if the antigen was there and define if it is a new [infectious] case.” [PI 1-Site2, SMO-3, SAVA-Mex, May-15-2015]

Although the researcher signposted that changes were accepted, the published protocol does NOT include the collection of a blood sample at day five for all participants, so his suggestion was partially accepted. To propose these changes, the local researcher had to convince the regional director of R&D about the veracity of his argument, as the next quote evidences:

“With Ernesto Reyes (SAVA regional director of R&D), I had the conversation about the antibodies... he asked me, where is that published? And I sent 200 papers, and they said, you are right, but this is the protocol, and we cannot modify it.” [PI 1-Site2, SMO-3, SAVA-Mex, May-15-2015]

SAVA’s regional director in this specific case acted as a boundary spanner-in-practice (Levina and Vaast 2014). He was not delegated to transfer information from researchers to the clinical team. In fact, no contributions from researchers were expected. However, this situation made it so that SAVA regional director assumed this role and regulated the flow of information between clinical researchers and the sponsor. The emergence of this boundary spanner-in-practice became a barrier across parts and knowledge provided by these researchers had to pass through filters before it reached the clinical team.

Published results about the vaccine indicates a problem with the introduction of the vaccine in Asia countries. Results indicate that the suggestion made by the Mexican researcher could have contributed to identifying, on time, the limitations of the vaccine, protecting people that had not had contact with the virus if a blood sample would have been collected after the first vaccination. Moreover, because the pharmaceutical company did not collect blood samples to all subjects over the course of the trial, the data collected is being re-analysed, and blood samples collected over the trial have been re-evaluated but not all data is available. Then this case shows how

academics can contribute to the project design. However, in the pharmaceutical industry, the fragmentation within the organisations and the emergence of boundary spanners-in-practice decreases the flow of knowledge between clinical teams and researchers. Therefore, clinical teams do not receive all the contributions of researchers for the trial design.

This situation shows how the sponsor did not expect a contribution from principal researchers, so they were not prepared to receive these comments. This point leads me to suggest that protocols could be shared with researchers in early stages, so their contribution can be analysed and considered with enough time. I do not pretend to suggest that principal researchers are always right and all their comments should be included immediately in the protocol. However, I consider it relevant to create a direct communication with the researcher and listen to their scientific suggestions, which can benefit the project.

In a clinical trial, the sponsor must obtain approval from each local regulatory agency to implement the trial locally. As part of these evaluations, local agencies have the right to provide comments and suggest modifications to the protocol. Nonetheless, clinical teams not always are open to receiving these comments and implementing them. I presented above how the NUSTAN clinical team was open to receive comments from researchers consulted to design the protocol. However, the NUSTAN clinical team was less permeable towards the recommendations made by ANVISA (Brazilian regulatory agency). The agency delayed the approval of the protocol and required additional information once NUSTAN submitted the protocol. After some deliberation between ANVISA and NUSTAN the agency requested the next information: “the validation of the PRNT Test, essential for the primary outcome of Phase II study, which has, for its aim, to evaluate the immunogenicity of each one of the 4 serotypes” (Porto 2015), and “the presentation of Phase I results obtained in the United States” (Ministério do Planejamento 2015). According to Dr Esmeralda, the agency was expecting that NUSTAN implemented the same PRNT validation approaches employed by SAVA in Brazil<sup>21</sup> and this was questioned for NUSTAN, as Dr Esmeralda pointed out:

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<sup>21</sup> ANVISA, as a regulatory agency, evaluated SAVA and NUSTAN protocols and SAVA's protocol was evaluated first.

“SAVA standardisation process for the vaccine is supported on premises that make sense in certain productive areas, but, (they) do not have sense in clinical areas. This generates confusions because they [SAVA] published that information (paper published by SAVA in 2013 about the PRNT), and that information ends up being a referent for the agency, but those things are questionable... There was that gap in the PRNT guidelines, and particularly when you reflect on this, I did not expect that ANVISA would assume that role. I think that ANVISA was not prepared in this sense to address those gaps in knowledge. Maybe a higher agency could have addressed better those gaps in the knowledge than a lower agency... It was collective learning for them and us; we found a middle point, and we got a dialogue between the parts.” [NUSTAN Chair, Apr-13-2017]

This quote expresses the frustration and discomfort of Dr Esmeralda with the agency for having used as a parameter the premises employed by SAVA to evaluate NUSTAN’s approximation to implement the PRNT test. But most importantly, this quote shows how NUSTAN call into question the agency’s knowledge and capacity to take decisions in situations when guidelines and standards have knowledge gaps. This quote evidences how the clinical team considered that ANVISA did not possess the knowledge to evaluate a protocol without any previous reference; the argument that was reinforced over the interview, as the next quote clearly indicates:

“Our regulatory agencies in Latin America receive multinational project approval from one of the major agencies of the world, the FDA or EMA. The Latin American country is just another country where the study is being done. Therefore, deciding on a project is easier because you [agency] already have the reference for the evaluation of an agency with greater experience... In our case, ANVISA was the lead agency, and this creates an unusual situation for them, they have to take a decision about something that they did not have a reference for, and that created doubts, enquiries, and in some cases, generates impasse.” [NUSTAN Chair, Apr-13-2017]

Then, this lack of trust in the agency made it that NUSTAN did not readily accept the suggestions and requirements made by this agency. Despite this lack of trust, NUSTAN had to present results about their test validation with some modifications, which indicates that they had to address some of the agency requirements and follow their suggestions. For this reason, the team was semipermeable to external comments because they had to negotiate and assess ANVISA comments. The low permeability in NUSTAN’s case, to external scientific knowledge, reflects elements of not-invented here syndrome (Katz and Allen 1982) because the clinical team considers that the external organisations do not have the capabilities and knowledge to provide accurate suggestions. For this reason, the knowledge received is not considered valid and the permeability of the team to include this knowledge in the protocol design is low.

Therefore, trust in the capacities of the source is an important element that mediates the permeability of clinical teams.

KINGE, located in the USA, received comments from the FDA to design its trials. KINGE's interaction with the FDA was quite different compared with NUSTAN's interaction with ANVISA. In the US, all sponsors considering the clinical development of any new molecule or biological product must register the new product as an "Investigational New Drug" (IND).<sup>22</sup> The product developer holds a pre-IND meeting with the FDA to review the information, and during this process, the FDA provides opinions and suggestions to improve the clinical plan. The next quote presents KINGE's experience about this meeting:

"First, we prepared a document called pre-IND that states – this is what I'm thinking to do. They give you feedback, and they say, I think that you are on the right track, or maybe you must reflect about this or that. After that, we have time to prepare the IND. [Sponsor- KINGE, Oct-25-2014]

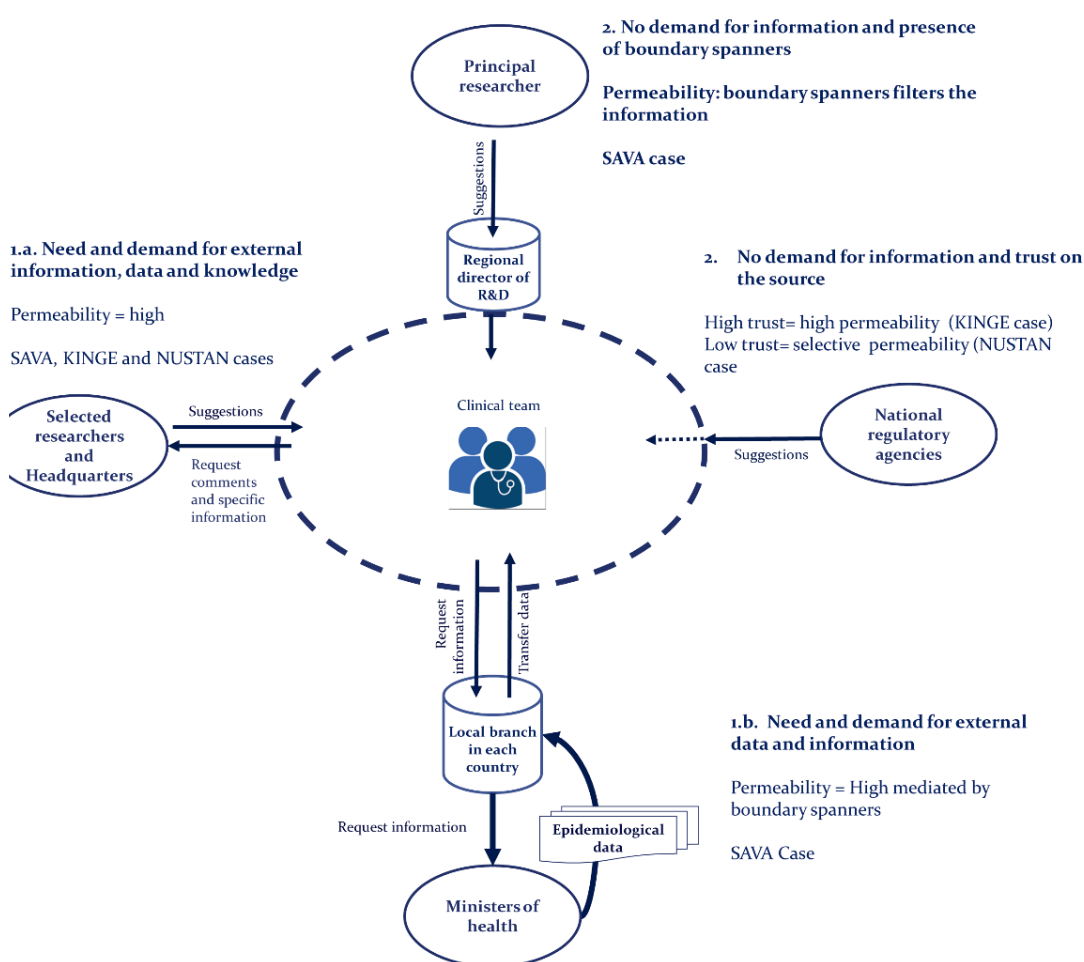
The narrative of the sponsor about the process indicates that they did not question the knowledge of the agency on the process and used the comments provided by the agency to improve the IND, showing permeability towards this source, which is contrary to NUSTAN's attitude of distrust of ANVISA criteria. Moreover, the sponsor considered that the agency had the right and authority to provide comments and they wanted the FDA validation of the trial. For this reason, the sponsor was open to adopting the agency comments. The expression "one always seeks approval from the FDA because many regulatory institutions worldwide follow the comments of the FDA" [Sponsor- KINGE, Oct-25-2014] shows that the power of the FDA over the sponsor is not only linked to their power to approve the protocol in the USA. The FDA power goes beyond the USA because agencies in other countries base their decisions on the comments provided by the FDA. Multinational companies know this fact, and they use the FDA power to their advantage to obtain approvals in the other countries; for this reason, they are also open to the FDA comments.

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<sup>22</sup> In the USA, any biological drug to be evaluated clinically in the country has to obtain the IND status; thus, this investigational new product can be used in humans and can be transported beyond the state borders for the clinical trials. The molecule dossier presented to the FDA has to contain information about animal pharmacology and toxicology studies, manufacturing information, and clinical protocols and investigator information (FDA 2000).

Then, as the NUSTAN and KINGE examples reveal, the regulatory agencies can have an active role in the design of a clinical trial. Their authority to allow the implementation of the trial gives them the right to question and request changes or additional evidence to implement the trial. However, their knowledge is not always considered valid or trustworthy by the clinical team and can be questioned, as the NUSTAN case exemplifies. So, both cases indicate that the permeability of the teams to external knowledge depends on how trustful and legitimate the clinical team considers the knowledge of the source to be.

**Figure 4. The permeability of the clinical team mediated firstly by the need for information, secondly by the presence of boundary spanners, and thirdly by the trust of the source.**



In summary, in this section, I have presented how the clinical team's permeability towards external information depended on three factors illustrated in Figure 4. The first factor is the demand for knowledge. Clinical teams were highly permeable to external



information, knowledge and data if there existed a need or demand for this data and information within the clinical team. This was the case of KINGE, SAVA and NUSTAN, who directly consulted the source, such as local researchers and the local branches (Figure 4-1.a) and they were open to their comments. Also, if teams demanded the information and used boundary spanners to access it, they were also open. This was the case of SAVA, who accessed databases of the health ministry through the headquarters (Figure 4-1.b).

The second factor that influenced the permeability of the team towards external knowledge and information was the trust that the clinical team had on the source. This factor played a crucial role in those moments where the clinical team did not demand knowledge (Figure 4- 2). Examples of this are the different openness of KINGE and NUSTAN towards the comments of their respective regulatory agencies. KINGE was open towards contributions provided by the FDA because they trusted the agency criteria; in contrast, NUSTAN was reluctant to accept the recommendations provided by ANVISA.

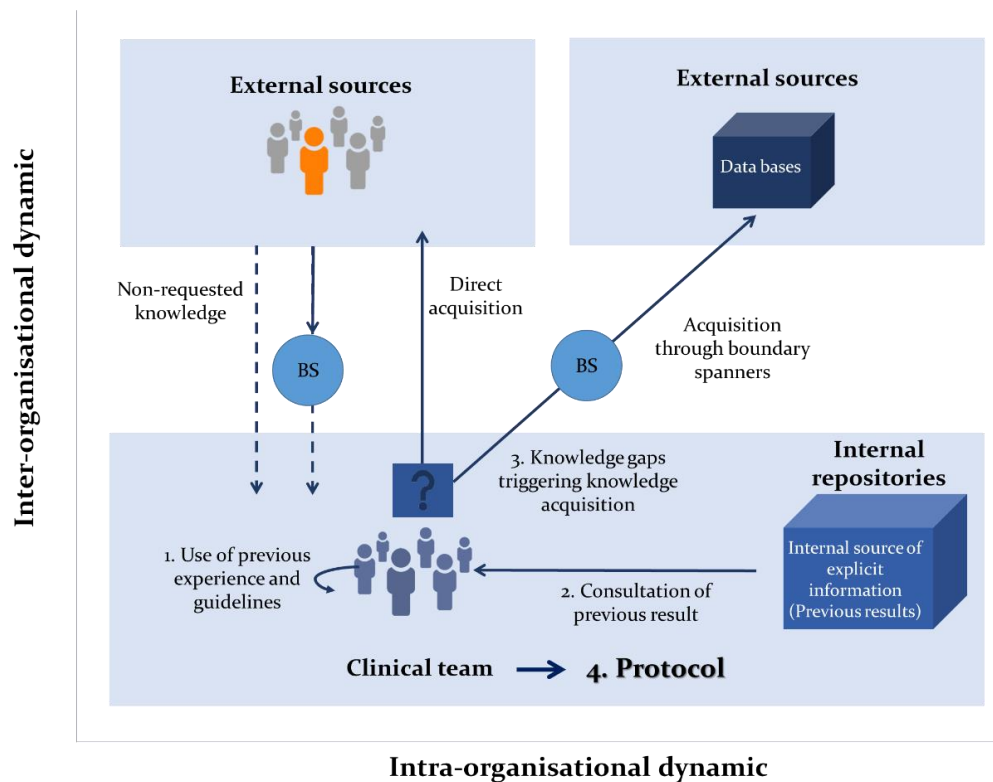
Finally, the third factor that influenced the permeability of the teams towards external information and knowledge was the presence of intermediary actors, who filtered the information and knowledge flow between the source and the clinical team. This was the case of the SAVA regional director of R&D, who regulated the communication between local researchers and the clinical teams, and also the case of the public affairs offices at the local branches (Figure 4- 1.b, 3). In the SAVA case, boundary spanners helped to get access to external knowledge, but also external actors acting as intermediaries between the team and researchers filtered unsolicited information from the research team, revealing the dual role of boundary spanners on the access and transfer of information as filters or information seekers.

## 4.4. Conclusions

This chapter aimed to answer the research question ***how did the sponsor acquire and use knowledge, data and information to design the clinical protocol?*** To answer this question, in the first section, this chapter addressed the intra-organisational dimension of the clinical teams to use knowledge, data and information to design the

protocol. In the second section, this chapter presented the acquisition of data and information to create the clinical protocol, discussing the team's permeability towards external sources. This chapter illustrates that the protocol design is not linear, and although clinical teams first employ their previous experiences, results and guidelines to design the protocol, the emergence of questions, and gaps in knowledge, data and information, trigger learning loops and the acquisition of knowledge data and information. In the end, the combination and use of their knowledge give place to the creation of the protocol. Figure 5 summarises the flow of knowledge to design the protocol, including the acquisition of internal and external sources of knowledge, information and data. Over the design of the protocol, not only medical, epidemiological, and regulatory knowledge and information is acquired and used to design the protocol. Knowledge and information about logistics in the endemic areas and the security conditions are needed to create the clinical trial, and the access and use of this knowledge and information reshape the protocol, especially the sample population defined for each site (Elements Table 3).

**Figure 5. Summary of the knowledge flow to design the clinical protocol by the sponsor.**



The results indicate that individual knowledge of the clinical team members was crucial for designing the protocol and the project (Figure 5-1). Almost all teams planning these projects had previous experiences doing this work, and they know how to do it using their professional and academic experience. Nonetheless, there are differences between sponsors according to their level of experience. The continuity of the clinical team members that worked on the previous project allowed a flow of knowledge from one phase to the other one. In this way, in interdependent projects, the knowledge acquired on the last clinical phases is preserved and used to create a new project. In contrast, in newly constituted clinical teams, the previous related knowledge provided a base on which to build new knowledge associated with the design of an interventional study, as the NUSTAN case illustrated, but the new clinical team had to make a learning effort to design a protocol and an entire project. For this, the new clinical team established a direct communication channel with personnel that worked on the previous trials.

As it was perceived by the people interviewed, it seems that designing the protocol was a simple process once they had all the information and data required. The evidence presented indicates that within the boundaries of the sponsor there existed the conceptual knowledge (medical, epidemiological) to design the protocol. The sponsor employed the information and data gathered from previous clinical and pre-clinical trials to create the new protocol, which is necessary for interdependent projects like the clinical trial phases (Figure 5-2). However, when the sponsor had cognitive gaps or required information, the team consulted external sources to acquire knowledge and information (Summary of the knowledge flow to design the clinical protocol by the sponsor. Figure 5-3). The experienced clinical team requested very precise data or information; in contrast, inexperienced teams searched for knowledge sources to teach them how to design the trial. In this chapter the concept of permeability was operationalised and evidence was presented regarding its relevance on the knowledge flow to create knowledge products.

The permeability of an organisation to external information depended on the demand of the team for it; unsolicited information and knowledge were less absorbed compared with data and information directly requested by the clinical team. As the data indicated, the openness to using this knowledge was mediated by the trust placed on the source. The cases of KINGE and NUSTAN provide a clear example of this openness. In the

NUSTAN case, the clinical team did not trust the knowledge of the agency to evaluate the project, and therefore, they were reluctant to address their comments in the first instance. On the contrary, KINGE trusted the comments provided by the FDA and consequently, the clinical team was open to adopting the FDA suggestions in their work.

The direction of knowledge acquisition is crucial because it determines the flow of knowledge and information, it modulates the interaction between the actors, and it influences the permeability of people towards external knowledge. In the case of SAVA, it was possible to differentiate between two types of boundary: nominated boundary spanners and boundary spanners-in-practice. Nominated spanners had the clear responsibility of searching, refining and transferring data residing in the health ministries and also, in contrast, boundary spanners-in-practice, who emerged because their role in connecting the clinical team and the local researchers became information regulators, filtering the knowledge and information suggested by principal investigators to the clinical team. In this case, boundary spanners controlled the flow of information between researchers and the clinical team, so information transferred had to be validated first by the boundary spanner.

# Chapter 5: Transition stage. Transfer and acquisition of knowledge and information from the sponsor to the research sites

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## 5.1. Introduction

In the last chapter, I discussed how the sponsor created the protocol using the information accessed from external sources and the knowledge accumulated by the clinical team. In this way, the clinical team transformed initial knowledge, data and information in a knowledge product. In this chapter, I will discuss the process to transfer the information and knowledge from the sponsor to the research sites, and the acquisition of this knowledge by the local researchers. In the model proposed, this chapter addresses the interdependency between the sponsor and the research sites, where the protocol and associated information is transferred to research sites to continue with their work and produce the clinical data. In the theoretical chapter, I discussed how the correct understanding and acquisition of relevant information to execute the task by the outsourced organisations is fundamental to the project's success. If the sponsor is capable of creating a shared knowledge about the project among all actors, the chances of project success are higher (Bustinza, Molina, and Gutierrez-Gutierrez 2010; Enberg 2012).

From the literature of knowledge management, three key factors were identified that influence the acquisition and transfer of knowledge to outsourced research groups or firms: (1) the sources and the channels of information, knowledge and data; (2) the permeability of individuals towards an external information and knowledge; and (3) the knowledge-base of the actors participating in the transfer/acquisition process. The identification of these three factors led me to the second research question of the project: ***To what extent does the structure designed by the sponsor to transfer knowledge, the permeability of the research sites, and the previous experience of***

*people working on the project influence the acquisition of knowledge in the research sites?* Therefore, in this chapter, I discuss in more detail how these three factors positively or negatively influenced the transfer and acquisition of knowledge and information by the research sites. Using the data of the three cases of study I address, at the inter-organisational level, the flow of knowledge among organisations in interdependent activities.

My data indicate that for each of the cases, these three factors have a distinct influence on the acquisition of new knowledge into the sites. The first section of this chapter discusses how the structural dimension of the transfer of information influenced the acquisition of knowledge within the research sites. Three elements mainly defined the structure of the network: the direct communication between the site and the sponsor, the outsourcing of the project to a CRO, and the outsourcing of the creation and management of research sites to SMOs. In the first place, the evidence indicates that, if the sponsor did not outsource the project to a CRO or there existed a direct communication channel between the site and the sponsor, sites received all the information required to implement the project. In contrast, in a structure where multiple intermediaries are present, the acquisition of knowledge and information by the site is slow because information is transferred incompletely and breaks in the communication among parts exist. Additionally, this section addresses the permeability of the staff towards external information. The data reveal that the sites' personnel were open to information transferred from experienced researchers or monitors that they trusted. In contrast, the staff were less receptive to the information transferred by monitors with limited experience in clinical research. The presence of multiple sources transferring information to the sites created confusion in the research group, so the evidence indicates that a low number channels employed to transfer information has positive benefits on its acquisition by the sites and the sites are more open to receiving the new information.

The second section discusses how the knowledge-base of the personnel working at the research site mediates the acquisition of information about the project and the key concepts of clinical research. In the first place, this section presents how specifically the regulation in Colombia determined the professionals that can work on the project, defining the professional knowledge that must compose a site. Secondly, this section

discusses the influence of previous experience (knowledge-base) on the acquisition of knowledge and the cognitive distance between the knowledge to be acquired and the knowledge residing on the site. As it will be discussed, experienced staff *on clinical research* had the practical and conceptual knowledge to understand the protocol; knowing the procedures to implement it and they knew what information to expect. So, these personnel had a knowledge-base from which they easily built their understanding of the project, the research product and the procedure. Thus, their cognitive distance regarding the knowledge required to execute the project was short. As it was expected, personnel that did not have experience working on clinical trials had to develop new knowledge about clinical research before being part of the project. However, the process to create this knowledge varied according to the research sites and previous experience as practitioners. In academic research groups, new staff were trained by their colleagues on the regulations and procedures to follow the GCPs, so the environment enabled them to learn the practical and conceptual knowledge to implement the trial. Whereas personnel working on new research sites were trained theoretically by the SMOs on the core concepts of clinical research, but all practical knowledge was without examples, so the lack of a learning environment decreased the speed to learn new knowledge. Despite the context of the research site, people with vast experiences as physicians, but without research experience, encounter more challenges in learning the practicalities of clinical research than people without any previous practical experience, which partially contradicts the argument that a previous knowledge base enables the acquisition of knowledge. What this evidence reveals is that previous conceptual knowledge enables the acquisition of conceptual knowledge, but some practical knowledge related partially to the activity to be undertaken can be an obstacle to learning new practical knowledge.

## 5.2. Structure to transfer information and its influence in the acquisition of knowledge by the research sites

In a clinical trial, the sponsor requires that all staff working on the project at the outsourced organisations understand the protocol and the task to be implemented. The validity of the data produced by the site depends to a large extent on the training of the personnel and their knowledge about the study protocol (Gassman et al. 1995).

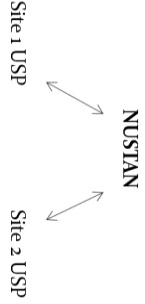

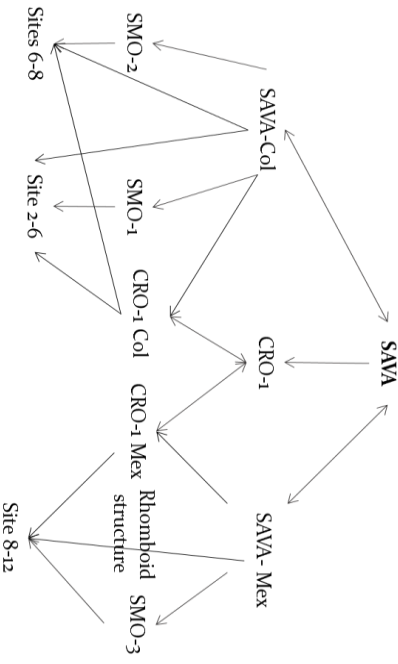
Research conducted by Subramaniam and Dugar (2012) emphasises the value of knowledge transfer and mentoring in the trials. Nonetheless, the acquisition of knowledge is not straightforward for the sites, as this section presents, where the channels and sources employed by the sponsor to transfer the information played a significant role in this process.

In the literature of knowledge management in outsourced projects, Blumenberg et al. (2009) indicated that the transfer of knowledge from one organisation to another has two dimensions: a 'content dimension' and a 'structural dimension'. The content dimension refers to the composition of the training and the documents transferred that have the concepts to understand the project. The channels, sources employed, and hierarchies to transfer the information, defined the structure to transfer knowledge among organisations and the hierarchies in the communication procedures, such as knowing whom to contact. In the three cases studied, the content dimension was similar, with some specific differences between cases regarding the proper procedures to implement. In all the cases, sites received information about the protocol, the vaccine, the management of the informed concern, the molecule brochure, manuals, the Standard Operative Procedures (SOPs) and Good Clinical Practices. In the particular case of SAVA, sites received training to manage communication media and how the principal researcher should proceed if he was called to provide a disclaimer in any legal case associated with a participant.

However, the structural dimension differed considerably across the three cases. Channels, sources and the protocols of communication from the sponsor to the sites were different, as is shown in Figure 6. In the NUSTAN case, the interaction between the site and the sponsor was direct. However, in the SAVA and NUSTAN cases, two factors influenced the structure to transfer information and knowledge from the sponsor to the sites. The first one was the outsourcing of the project to a CRO; the second one was the outsourcing of the management of research sites to SMOs. Each one of these structures had a significant impact on people's acquisition of knowledge and on the flow of information over the course of the trial.



**Figure 6. Structural dimension for the transfer of information for each one of the cases studied employed by each one of the sponsors to transfer information to the research sites.**

Factors defining the structure				
Managing of the project through a CRO	Outsourcing of the research sites through a SMO	No	Yes	Yes
				

### 5.2.1. Direct communication between the sponsor and the research site

The outsourcing of the management of the project to a CRO is the first factor that determined the structure for the transmission of information (Figure 6). However, of the three cases, the NUSTAN case was the only one that did not outsource the project to a CRO. This decision benefitted the transfer of information and training of the personnel about the protocol, as I will explain. In the NUSTAN case, the communication between the sponsor and the sites was direct. The sponsor trained the staff at the research site on the protocol and procedures, as one of the sub-researchers and NUSTAN Chair said:

**Quote 1:** “We had the protocol specific training, some of them were provided by the sponsor.” [Sub-Res-USP, NUSTA, Apr-14-2015].

**Quote 2:** “We teach the team about the research product, what the product means, what the clinical development plan means [...], how clinical research works, more from the conceptual standpoint than the formal one, the management of the archive of the monitoring system.” [NUSTAN Chair, Apr-13-2017].

Also, in NUSTAN’s facilities, all sites’ data managers were trained to use the software. All this training was face-to-face, which allowed a direct communication, and all the questions that emerged were resolved *in situ* and on time. NUSTAN decided not to outsource the trial monitoring to a CRO, and they created an internal monitoring team to evaluate the site performance and provide feedback. Regarding this specific activity, the sponsor had a clear vision about the monitor’s role in transferring knowledge:

“Monitoring activities are oriented on building the site, on explaining why [something occurs]. This [monitoring] is not a witch hunt; this is about teaching what it means clinical research and why the procedures are done in a certain way... Monitors are not rewarded for finding many mistakes; on the contrary, if they find many mistakes it is because they [monitors] are not doing well their job... All training provided has to be focused on explaining to the centre why they are doing that; it is not ‘this is not what you have to do’.” [NUSTAN Chair, Apr-13-2017]

Over the course of the project, the monitor provided training to the site personnel, as the quote indicates. This training focused on explaining the scientific basis of the protocol. In this sense, the research sites learned about the logic behind and scientific rationality of the task stated in the protocol. This approach differs to the other cases where monitors provided training on the process and reviewed operative information.

For the NUSTAN Chair, personnel at the research sites needed training on specific aspects related to the trial and data management, and they did not need training on how to manage patients, as is clear in the next quote:

“I think that we do not teach them how to manage the subjects. On the contrary, they teach us. We do not have that pretention; we are not clinicians there in the front line, they are, they know much better than us. This is for sure.” [NUSTAN Chair, Apr-13-2017]

Then, the NUSTAN clinical team had confidence in the knowledge of the sites related to the management and care of participants. Thus, there is a real trust in the site capabilities by the sponsor to implement the protocol. Therefore, the NUSTAN case shows the interest of the sponsor on transferring a substantial knowledge about all aspects of the project establishing direct communication with the sites.

In the cases of SAVA and KINGS, although the sponsor delegated some of the training to the CROs and SMOS, in both cases, an *investigation meeting* took place *before initiating the project*. At this meeting, the sponsor directly interacted with the principal researcher of the project and staff to explain the project and the protocol. However, not all information was transferred in this meeting (Following sections 5.2.3). In the case of KINGS, in this meeting, the site’s personnel were trained in the conservation of the vaccine’s cold chain,<sup>23</sup> informed consent, the vaccine and the protocol. Additionally, the sponsor outsourced the training on GCP to an organisation that provided online courses, which is a common practice in the industry<sup>24</sup> and also was employed in the SAVA case.

Similarly, in the SAVA case, at the beginning of the project in Colombia and Mexico, the local branch, the CRO and the SMO coordinated meetings with the sites to provide training.

“All the principal investigators are invited to this meeting, one sub-researcher and the trial coordinator (per site). There they are taught everything, they are trained

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<sup>23</sup> “The purpose of the vaccine’s ‘cold chain’ is to maintain product quality from the time of manufacture until the point of administration by ensuring that vaccines are stored and transported within WHO-recommended temperature ranges.” (WHO 2015)

<sup>24</sup> The pharmaceutical companies have been working on creating a unique GCP training for the industry under the frame of the Transcelerate biopharma initiative, so a site does not have to do a different course for each sponsor, saving time because sites will not need to complete duplicate training.

in the molecule, in the protocol, in the operational guides, in the diaries, in everything that is going to be used in the study, they are trained there (meeting). And then, there is an opening visit; it is close to when we are going to start the study when the first patient is going to be included. In the research site, the rest of the staff is trained in everything related to the protocol.” [SAVA-Sponsor Col, Mar-24-2015]

“The initial training was on the protocol, and on the selection of the volunteers etc. The second part was about the process to take the (medical) notes, how to fill out the files, and how to be careful with the deviations. The last training was about details where we learn how to adhere the subjects, what it is and what I can use and what I cannot use to avoid misunderstanding.” [PI-Site3, SMO-3, SAVA-Mex, Jul-08-2015]

For the opening visit, in both countries, the CRO, the local branch and the SMO travelled to each one of the research sites as the two quotes suggest. The content of the training covered the protocol, the vaccine’s cold chain, the informed consent, the molecule brochure, the management of the database, sample handling, file management and participant follow-up, and management of protocol deviations. In these meetings a face-to-face interaction between the parts took place, and it created an initial understanding of the project by the research site personnel, as the second quote points out.

One can conclude that these investigation meetings are common practices across the pharmaceutical industry, which allow the transfer of knowledge and information from the sources (sponsor) to the research sites. These meetings set the basis for the research sites to implement the protocol-interdependent task, following the instructions and guidance provided by the sponsor, the CROs and the SMOs (if they are present); in this way a shared knowledge about the project is created. A number of researchers have reported the relevance of initial encounters between contractor and supplier in transnational and outsourced projects to enable knowledge creation and sharing (Adenfelt and Lagerström 2006; Bhalla and Terjesen 2013; Samoilenko and Nahar 2011). It has been argued that face-to-face meetings enable the co-creation of a shared meaning and understanding of the project between the distributed actors, which is more challenging, employing information technology (K. Kumar, van Fenema, and von Glinow 2009). The fact that the sponsor did not delegate the transfer of this content to a CRO indicates the relevance of this knowledge for the project, and how, despite the presence of other communication channels, in vaccine clinical trials, the specific

knowledge about the project is received by the research that sites receive from the lead organisation. Therefore, in a multi-organisational project, bringing together the project members in the investigation meeting is essential for the execution of interdependent task because it allows direct communication among the parts and these personal channels (Mandják et al. 2015) allow the transfer and acquisition of procedural and conceptual knowledge.

### 5.2.2. Influence of the outsourcing of the clinical trial management to CROs

In the SAVA and the KINGE cases, the sponsors in the headquarters decided to outsource the management of the clinical trial to CROs, which included outsourcing part of the project training. This decision determined the communication structure and hierarchy to transfer information from the sponsor to the sites, and it had consequences on the acquisition of knowledge by the research sites. The reason to outsource the project varied between the two cases. In the case of KINGE, the firm did not have branches in Colombia and in any of the countries where they implemented the trial. Therefore, they decided to outsource the coordination of the trial to the CRO-1, which acted as the sponsor's legal representative in Colombia and the other countries. As Dr Jaime Plata (KINGE sponsor) stated: "The CRO was in charge of everything, of everything at a particular cost." The CRO was responsible for the entire coordination of the trial, including:

"Local trial insurance, the importation and conservation of the cold chain of the clinical product (vaccine), the exportation of biological samples, data management, monitoring of research sites,<sup>25</sup> verification of audits to the sites, verification of national and international standards fulfilment, training to the sites, and submission of the protocol to the national regulatory agency." [Monitor-CRO, KINGE-Col Nov-27-2014]

Although KINGE had a previous and a direct relationship with the sponsor, the linkages between actors were redrawn at this transition stage. Over the training and project implementation, the sponsor interacted directly with the CRO's headquarters, the headquarters with the local CRO and these with the site (Figure 6 – KINGE). Then, "if

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<sup>25</sup> Monitoring is the act of overseeing the progress of a clinical trial, and ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and the applicable regulatory requirements.

the sponsor decided to send specific information to the research site or anything, the sponsor would send it to the CRO, and then the CRO sends it to the research group” [Monitor-CRO, KINGE-Col Nov-27-2014]. So, the sponsor established a linear structure to transfer information using the CRO as an intermediary, which is one of the most common structures in the pharmaceutical industry nowadays, primarily to coordinate the multi-national projects in cases where the sponsor does not have branches in all countries. Therefore, in this case, the structure created to train the site in the interdependent task had two components: a direct channel sponsor site and the intermediation of the CRO to transfer information.

Although SAVA had branches in Colombia, Brazil and Mexico, the headquarters decided to outsource the management of the trial to a CRO like in the KINGE case, but in the SAVA case, the objective was to decrease the cost of the monitoring process and get the CRO’s support on the management of the local regulation. In addition to the CROs, the sponsor decided to outsource the creation of new sites and the training of new research staff to SMOs in Colombia and Mexico because of the lack of research capabilities in endemic regions (high prevalence of the disease) where SAVA needed to implement the trial. Then, the outsourcing of the coordination of the research sites to an SMO was the other factor that defined the structure to transfer information from the sponsor to the sites to implement the clinical trial. This outsourcing generated a structure where multiple channels were employed to transfer information (Figure 6 – SAVA) which directly influenced the acquisition of knowledge and information by the research teams (a point addressed in section 5.2.3).

In the case of SAVA, the structure to transfer the information from the sponsor to the sites had two ramifications where the CRO was part of the structure. In the first place, the headquarters transferred the information<sup>26</sup> to their local branches, the regional team and the central CRO. Then, the central CRO transferred the information to the local CRO (Ramification 1). Locally, SAVA’s local branch and the regional team trained the SMOs on the protocol (Ramification 2). Then, in turn, the local branches, the SMOs and the CROs cooperated to transfer the information to the sites and train them on the

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<sup>26</sup> The protocol, vaccine, informed consent, molecular brochure, manuals, Standard Operation Procedure and Good Clinical Practices.

project (Figure 6 – SAVA). For example, one principal researcher in Mexico said: “the training was provided by the three, SAVA, CRO [name], and the team of Dr Agáta [SMO-3]” [PI-Site 4, SMO-3, SAVA-Mex, Jul-09-2015]. Then, as it is possible to see, the transfer of information from the clinical team to the research sites was complex and with the presence of multiple actors providing overlapping training.

The interviews indicated that the presence of the CROs (SAVA and KINGE) and SMOs (SAVA) created difficulties in the information transfer because of the complexity of the structures created. One of the shortcomings of outsourcing the transfer of information to the CRO is that the CRO’s monitors do not always transfer all the information to the sites. In an audit contracted by KINGE, the auditor found that the monitor did not send all manuals to the sites to execute specific tasks, blocking the information flow:

“With the audit, we knew that there were documents that monitors were not given to us, why? We don’t know. The monitor had these ones, but we did not even know about their existence, so there was a gap in the information.” [PM2 R-IDVI, KINGE, OCT-22-2014]

Moreover, over the course of the trial one project manager reported how she had to request information to the monitor because she omitted it:

“As you get experience and you know which the necessary documents are, then you can request these to the monitor. They [monitors] many times don’t send you all the information. In my case I had to ask the monitor for many documents because she did not send those to me, she forgot it, or she did not have it.” [Project Manager, R-IDVT, KINGE]

These two quotes indicate two important facts about the presence of the monitors as intermediaries in the transfer of documents. The first one, the gaps in the transfer of information from the CRO monitors to the sites. And the second one, that monitors sometimes do not have the information requested, as the last expression of the last quote seems to suggest. This delay in the transfer of information seems to be associated with the complex structure inside the CRO to transfer information within the organisation, affecting the information flow from the sponsor to the site through the monitors, as SAVA’s project manager in Colombia explained:

“The CRO have their monitors in Colombia [also in Mexico], they [monitors] have two bosses. One that is the lead manager that manages all the human resources and training and reviews your work locally, and they have a project manager that can

be located in Europe, Brazil, Colombia or Mexico, wherever they want, and he is responsible for the project advancement. [...] Then, they have a structure that is so complex, many times the monitor is alone without knowing what to do [...] It is necessary to review how the structures generated are efficient, most times they are not, why are they not? Because negotiations are centralised, I do not do it. Headquarters consider ways of work in the United States and Europe, but here we work differently; sometimes it works, some other times it does not.” [SAVA-Sponsor Col, Mar-24-2015]

So, in the SAVA case, as this quote points out, the presence of an intermediary organisation like the CRO affected the transfer. The fragmented structure within the CRO to communicate the information among the personnel working for the project distributed geographically seems to explain why the monitors took longer to receive all the information sent by the sponsor. The SMO-2’s project manager, Manuela Figueroa, in Colombia, also considers that the presence of the CRO does not benefit the project; in contrast, it makes the process slower and without the guarantee that sites will produce the data under the standards demanded by the sponsor. She worked for Merck doing clinical research, and she considers that the sponsors “had developed a series of norms and tools to ensure that the sites were complying with their requirements” [OM SMO-2, SAVA-Col, Dic-03-2014]. Then, according to her view, there is no need to outsource a project to a third party.

The emergence of the CROs as intermediaries in the transfer of information took place in the context of Latin America countries around fifteen years ago. Before this period, the pharmaceutical companies had their monitoring departments and controlled the training, transfer of documents and all monitoring activities of the trial. However, as the sponsor in Colombia explained in the interview, “between the 2009 and 2010 the industry in Colombia changed and everything is outsourced to a CRO”. This change in the industry demanded from the companies a change in the way in which they coordinated projects and how to engage with a third party, the CRO. In SAVA’s view, this was not easy, and they lost control over the sites and the monitors because of the additional management layers. Before internal monitors established the working conditions in the sites, now these activities are delegated to a CRO, and the sponsor has low control over the monitors’ training as the next quote indicates:

“If I [sponsor] say: that the monitor has low performance, the country lead manager [CRO] is the one that intervenes. What is the low performance? He does not know how to report deviations. So, the lead manager is the one that trains him on how to



do reports, but he has to have the project manager over to tell him how we (SAVA) need the project. These are complex structures where many times the monitor is alone without knowing what to do, and we particularly get involved in the process.” [SAVA-Sponsor Col, Mar-24-2015]

It is a fact that the sponsor’s motivation for decreasing costs associated with labour force influenced the outsourcing of monitors to the CRO. However, comparing the experience of NUSTAN not outsourcing the project with the experience of KINGE and SAVA outsourcing the trial to a CRO, it seems that this change in the industry is creating multiple gaps in the transfer of information from the sponsor to the sites rather than benefiting the efficiency of the project execution, speeding the transfer of information and supporting the work of the research sites. As the last part of the quote points out, this outsourcing demands a direct involvement from the sponsor on the training of the monitors, which requires an investment in time from the sponsor on training monitors; training that the CRO should provide internally to the monitors.

There is a trend on outsourcing training in organisations for their personnel (Gainey and Klaas 2003), and some questions have been raised about how effective it is to outsource this activity. Geldenhuys et al. (2012) expressed their fear of outsourcing staff training in a clinical trial to a third party where there is a risk that trainers do not understand the target audience or they do not identify knowledge gaps in the staff to correct them on time. Moreover, Smed and Getz (2013) pointed out how the presence of CRO restricts the transfer of lessons learned at the end of the trial between the site and the sponsor. The evidence presented in this section shows that the presence of the CRO can also have a detrimental influence on the transfer of information and knowledge at the beginning of the trial, which is aligned with the concerns expressed by Geldenhuys et al. (2012). Complex structures at the intra-organisational level in the CROs also create gaps in the knowledge and information that the monitors receive, necessary to do their job. Then, the combination of complex intra-organisational structures and inter-organisational structures have a negative consequence on the transfer of information in the knowledge-intensive project (KIP). So, these gaps, in the long term, can have an impact on the execution of the project and the way in which information is accepted or not by the research sites, as will be discussed in the next section. Therefore, if the presence of the CRO does not contribute to the quality of the research and blocks the flow of information between the sites and the sponsor, it is

necessary that the sponsor reviews the structure employed to transfer the information and to manage the sites over the course of the project.

### 5.2.3. Influence of the outsourcing of the management of the clinical teams to SMOs

Continuing with the discussion about the influence of the structural dimension on the transfer of information from the sponsor to the sites, the second factor that influenced the transfer of knowledge was the outsourcing of the site management to SMOs. This outsourcing created a complicated structure to transfer information, as Figure 6 – SAVA shows. In the SAVA case, the CRO and the SMO were the primary sources of information to the research sites, also having overlapping responsibility for training and supporting the sites over the course of the project. On the one hand, the SMOs in Colombia and Mexico **created the research sites and trained them** on all the aspects related to clinical research and the execution of projects. The SMOs provided collective training and solved any questions about the project before it started, and the sites regularly consulted the SMO over the course of the project.

On the other hand, the sponsor hired the CROs' monitors with the vision that they should be the 'site manager', as SAVA's project manager in Colombia indicated. For SAVA, the monitors should provide training and feedback to the sites over the course of the project based on the results of the monitoring activities. According to Fernando Amatista (Regional Manager, SAVA-Mex), the presence of the CRO and the SMO was conceived by the sponsor to provide continuous support to the sites; however, in practice, this was not the case. Sites trusted more in the information provided by the SMO rather than in the feedback or initial information given by the monitors (this is discussed below), and sometimes, sites were confused because they received contradictory information via these two channels. The next quotes illustrate part of the conflict and clashes in the transfer of information experienced because of this 'double channel structure':

**Quote 1: "Interviewer:** Have you perceived that they doubt your knowledge?

**Monitor:** At the beginning, because I did not have experience, also as there was the SMO in the middle, always were... we said something and they had to escalate it to

the SMO, so there was a clash of opinions, nonetheless, nowadays what we say generally has validity.” [Underlining added, Monitor-CRO, SAVA-Col Dic-10-2014]]

**Quote 2:** “Then, if you are new [monitor], you are fussier because you doubt everything, then everything was a deviation. We said this is not a deviation, we did a reflection, and we discussed with the coordination, [SMO said] ‘OK if you don’t agree you can tell them’, ah, OK, then they [SMO] started to mediate.” [Underlining added, PI-Site 4, SMO-3, SAVA-Mex, Jul-09-2015]

**Quote 3:** “You can request advice, but to the monitors not, let’s say that they are at a very lower level, they have to do their monitoring work and that is all.” [OM SMO-2, SAVA-Col, Dic-03-2014]

The three quotes show, from the perspective of three different organisations, the conflict that emerged because the presence of the SMO and the CROs transferring information and providing suggestions. The first quote shows how the monitor experienced a barrier from the site because the SMO was present in the project. This barrier impeded that the research site easily accepted his suggestions. The second quote illustrates the perspective of the sites and clearly shows a preference for the opinions of the SMOs and a distrust of the recommendations of the monitors. And finally, the last quote shows the position of one SMO about the role of the monitors, where she considered that monitors did not have the level to provide advice, so in her view, they were not qualified to train the sites.

This last point lets me suggest that the structure designed by the sponsor to transfer the information and the trust in the sources modulated the permeability of the research sites towards external sources. In this thesis, I proposed the concept of permeability based on the discussion in the literature about knowledge acquisition and trust (A. K. Gupta and Govindarajan 2000; Katz and Allen 1982; Grosse Kathoefer and Leker 2012; Lichtenthaler and Ernst 2006). I defined permeability as the motivation of people working in an organisation to accept or not the knowledge and information coming from outside its boundaries. The three previous quotes clearly reflect that sites were less open to accepting information transferred by the CROs, so they had a low permeability towards this source. As quote 1 suggests, the fact that sites received information from the CRO, and the SMO, made the site’s staff less permeable towards the source in which they trusted less and inspired less confidence; the CRO. As quote 2 indicates, the staff at the research sites considered the SMO more qualified to provide advice, for this reason, the site’s staff trusted on the SMO and were more permeable to

their comments and suggestions. Also, the expression, “they are at a very low level” in quote 2 indicates how reluctant this SMO was to the feedback provided by the monitors. This quote suggests that, for this SMO, the monitor did not have the knowledge or even the responsibility to provide feedback to the site, which in turn meant that their sites were less permeable to the monitors. Then, this evidence contradicts the vision of the sponsors in Colombia and Mexico, which considers that the monitor should be the manager of the site and that a joint work of the CRO and the SMO supported the research sites. In fact, the presence of these two actors on the ground created a contrary effect. Therefore, this evidence indicates that complex structures to transfer knowledge, where more than two channels are employed to transfer similar information, creates confusion in the sites because they must decide on who to believe and how to raise any issue, as quotes 1 and 2 exemplify. In summary, having two different channels of information with overlapping functions rather than providing support to the sites created conflicts and insecurities in the sites and affected the acquisition of knowledge. Then, the sponsor at the headquarters (they design the project structure) must be careful in the structure employed to transfer the information to the sites avoiding the outsourcing of related tasks to two different organisations such as the SMO and the CRO. In this way, the sponsor enables the acquisition of knowledge and makes clear the responsibility of each actor during the training and over the course of the trial.

The evidence collected indicates that the permeability of the research sites towards monitors changed over the course of the trial, sometimes shifting from open to closed, and other times from closed to open, which indicates that permeability is dynamic over the course of the trial. This dynamism depended to a large extent on the trust in the sources and the confidence in the knowledge residing within the research team. In Mexico, one site working for SAVA explained how the first monitor assigned to be with them in the project “inspired confidence” because she had experience, so they followed her advice. However, in Mexico at the beginning of the project the turnover of monitors was recurrent, so, this monitor left the project. The information transferred by the new monitor was accepted and followed at the beginning by the site without being questioned, which suggests an openness of the team toward this source. But later on, this information was questioned by the site because it contradicted the knowledge

acquired from the previous monitor and the knowledge that they had gained in practice. Therefore, after evaluating the situation they decided to trust in their knowledge, and they did not follow the monitor's advice anymore. As the principal researcher said:

“At the begging, we said yes, yes, yes to everything, because we didn't know how to say NO. At one point we said that is an excess, then we recognised ourselves, and we also had the power to say this is in this way, and I do not agree at all.” [PI-Site 4, SMO-3, SAVA-Mex, Jul-09-2015, underline added].

So, this case exemplifies how a team can change the permeability towards the information provided by the CRO, passing from open – accepting the feedback provided by the monitor – to closed – rejecting his advice and trusting in their knowledge – because trust in the source decreased and they started to value their knowledge more.

Data collected in Colombia also show that the staff permeability towards the CRO's monitor also changed from closed – less receptive to the external knowledge – to open – being more receptive to suggestions. One of the monitors explained that he was determined to prove to the sites that he had the knowledge and skills to provide feedback. He was the same monitor that expressed in one of the quotes above that sites did not trust in his knowledge at the beginning because of his lack of experience. However, it seems that the site reacted to his work and they were more open and learned from the monitor, as Dr Perla said when he explained to me the evolution of the relationship between the monitor and the site:

“We have learned a lot from them and they from us. We know the day to day of the site, and they have the macro knowledge of the process, then there is a knowledge exchange, and this helps us to make sure everything goes well.” [PI-Site-1, SMO-1, SAVA-Col]

Therefore, the data presented indicate that the low permeability of the teams towards external information or knowledge is not only associated with not-invented here syndrome (Katz and Allen 1982) in which receptors reject knowledge because of envy, jealousy or power. Together, these results suggest that receptors' permeability towards external information depends on the evaluation that the receptor does about the source, of his experience and on the trust built as the project advances. The positive influence of building trust on the evolution of customers' and suppliers'

communication has been discussed (Gainey and Klaas 2003). These findings are consistent with those of Park et al. (2011) and Lee et al. (2008) in the IT industry, and the results of Maurer (2010) on engineering projects, which indicates an association between trust and the sharing of knowledge and acquisition of knowledge. According to the results of Lee et al. (2008), mutual trust increases the confidence among the parts achieving common goals, which were the case of some research sites visited, which reported that as trust increased in the monitors, the number of deviations decreased and the work was harmonic, reducing the uncertainty in the relationship. Also, results in this thesis support the results presented by Maurer (2010), which indicate that a stable pool of project team members facilitates the formation of inter-organisational trust. The fact that CRO's monitors changed over the course of initial phases decreased the possibility of creating stable bonds between the research site and the CRO, affecting the acquisition of knowledge. This situation differs to the stability between the SMOs and sites where personnel were constant, and the parts built trust. Therefore, sites were permeable towards the SMOs. Then, inter-organisational relationships require cultivation, and relational investments to achieve sustainable benefits for the project and promote the transfer and acquisition of knowledge over the course of the project.

In this section, I have addressed the structure that each sponsor created to transfer information to the research sites and its influence on the acquisition of information and knowledge by the research sites. In the first place, in the case of trials in Latin America, it is a fact that the presence of the CROs and SMOs has changed the training dynamic between the site and the sponsor. The presence of these actors decreases the interaction between sponsor-sites and affects the flow of information and knowledge across the two parts and the acquisition of knowledge by the sites negatively. Gosain et al. (2004) presented how the transfer of a large amount of information is detrimental to the vendor-supplier relationship and the creation of mutual understanding. What the SAVA case shows is that in addition to the quantity of information transferred, the channels selected to transfer this information, the quality of the information and the number of channels are critical to ensuring the correct acquisition of knowledge in outsourced and interdependent projects. A complex structure to transfer information and knowledge with multiple intermediaries representing the sites caused a conflict and confusion in the sites because they received contradictory information and they

had to select one source in whom to believe. Therefore, a simple structure with direct communication between the sponsor and the sites is better to transfer the information. Previous research on the transfer of knowledge has suggested that flexibility and informal interaction are preferred in the initial stages to give time for the relationship to develop and generate strong interpersonal trust across organisations (Narayandas and Rangan 2004). The evidence in this section indicates that trust is fundamental to the acquisition of knowledge and information. However, to transfer information in within a complex structure, it is preferable to establish defined clear roles and responsibilities rather than have informal interactions, especially in those cases where overlapping responsibilities exist.

### 5.3. Previous experience and the acquisition of new knowledge

In a clinical trial, the research sites are those that execute the protocol, and for this, they employ the knowledge residing in the organisation. The regulations in Colombia, Brazil and Mexico (Ministerio de la Protección Social 2008; Ministério da Saúde-ANVISA 2008; COFEPRIS 2012) and the ICH guidelines establish that all workers must have the qualifications to be part of the project (ICH Harmonised Tripartite Guideline 1996:44). The curriculum vitae and/or other relevant documents of each person working on the trial had to evidence his/her qualifications to execute the task delegated. It is common that sponsors operating in Colombia, Brazil and Mexico recruit experienced principal researchers<sup>27</sup> or experienced research sites, so they can be sure that the personnel working on the project are qualified for the trial.

In chapter 2, I discussed how people's previous knowledge is considered a condition to acquire and introduce knowledge to an organisation (Li et al. 2014; Nooteboom et al. 2007; Cohen and Levinthal 1990). The cognitive bases of people are relevant because they condition the acquisition of new knowledge in the sites. People learn to associate previous knowledge and experiences with the knowledge and information received

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<sup>27</sup> Information obtained from interviews with clinical trial associations in these three countries: much of the protocols do not need a team; individual physicians implement the protocol and have an assistant that submits the information. The evaluation of vaccines is different in the fact that these trials demand a large population sample. Therefore, these trials are outsourced to research sites with multiple physicians and support staff to manage the multiple activities that demand recruiting and following up these populations.

(Cohen and Levinthal 1990; Nonaka 1994). There is a group of scholars that argue that teams, to some extent, adapt easily to new situations as a result of their shared experience (Hollenbeck 2012). For this reason, experienced teams differ from new teams in performance and learning because mature teams have more experience as a result of a cyclic process of learning and feedback (Savelsbergh, Poell, and van der Heijden 2015, 407).

In this thesis, the teams implementing the protocol receive the name of research sites. However, it is important to note that between these research sites there existed substantial differences in the level of experience and the size of the team. Also, within teams, there existed clear differences in the experience of the personnel. Therefore, in this section, I will discuss how the previous experience of team members conditioned the acquisition of new knowledge, and how new sites acquired new know-how before the clinical trial. In this section, I make a distinction between experienced research sites and new research sites and how, in each one of these groups, new personnel acquired new knowledge. In the end, I discuss how previous know-how rather than enabling the learning of new practices, presented a barrier to acquiring new knowledge and using it to execute the trial.

### 5.3.1. Experienced research sites and the training of new members within the research site

KINGE and NUSTAN outsourced the execution of the trial to research centres located in universities in Colombia (R-IDVI- KINGE) and Brazil (University of Sao Paulo, USP- NUSTAN) both led by well-known researchers in the field of infectious diseases in each country. The size of the team was between five and ten members, and the number varied according to the project stage.<sup>28</sup> Both sites had more than 20 years of experience conducting clinical trials, and also the site had previous ties with the sponsors, who knew about their experience. For example, the research group R-IDVI- KINGE had implemented trials for the WHO validating a leishmaniasis drug 22 years ago. Moreover, the group at the USP also has more than 25 years of experience working on clinical research and has vast experience in HIV research. On both sites, the principal

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<sup>28</sup> At the recruitment stages the number of physicians, nurses and social workers is higher than at the end of the project.



researcher, the project manager and quality assurance staff have been working with the group over ten years, implementing protocols. Therefore, they knew how to implement the project, and they had developed a collective understanding of how to conduct clinical research. Then, as Dr Jaime Plata (Sponsor KINGE) said: “The research groups have people well qualified with high experience in the implementation of clinical trials. Also, they have a knowledge of the disease, which makes it easy to work with them.”

Experienced staff working at the USP (NUSTAN case) and R-IDVI (KINGE case) had the specific medical, technical, and regulatory knowledge that allowed the implementation of the trial, fulfilling the regulatory requirements, and producing the data with the quality demanded by the sponsor. Expressions like “[previous experience] was very instructive because I could understand a lot of the processes and how to take a program project forward” [PI-USP, NUSTAN, Apr-01-2015] or “[KINGE] presented to us the project and we saw it was viable under the required conditions” [PM R-IDVI, KINGE, Nov-05-2014] reflects that personnel at the sites and the principal researcher had the knowledge to understand the project, acquire the information transferred by the sponsor or the CRO (KINGE case) and also the know-how to implement it. Also, as I presented before, the previous experience of personnel at the KINGE site allowed them to identify gaps in the information transferred by the CRO. Therefore, this previous experience permitted them to understand the project, as the last two quotes indicate, and enabled the knowledge transfer and acquisition.

Nonetheless, both research teams had personnel without clinical research experience. The people interviewed in these sites had the professional background to perform the task delegated (pharmaceutical chemists, physicians, data managers), having knowledge bases to acquire new knowledge. New staff in the USP and the R-IDVT sites reported that learning was simple because the academic environment of the group enables them to create knowledge bases for the new personnel participating in clinical research. In both academic groups, a regular activity was group meetings and study groups to discuss academic papers related to the project under execution. Then, in these activities, they expanded their conceptual knowledge base, as sub-researcher in the USP and R-IDVT group explained:

“Every month we have a group reunion, and at the end, we discuss some articles, some things interesting in the research program with the coordination of Dr. [João].” [Sub-Res-USP, NUSTA, Apr-14-2015]

“The medical practice of a general practitioner is very different to (doing) research. I as a general physician did not read the results of a new study, but when you are doing research you study about how it was done, you analyse the information, and you know why you are doing it. But it is only when you start doing this that you learn.” [Sub-Res, R-IDVI, KINGE, Nov-05-2014]

Therefore, as the quotes show, this academic context enables the extension of the knowledge bases of the members, to understand the projects in which they are working.

However, these new staff were not familiar with how to implement the project; then they had to learn how to do clinical research. Although the sponsor and the CRO (only in the KINGE case) trained them on the protocol and specific procedures of the project, these new staff learned the know-how necessary to implement a protocol within the research site boundaries. Like Leonardo Silva (data manager working for USP site) and GP David Vega (sub-researcher at the R-IDVT site) narrated:

**Quote 1:** “Most of the staff working on clinical research did not learn [clinical research] at the University, they learn when they arrive to work... they learn everything.” [DM-USP, NUSTAN, Apr-13-2015]

**Quote 2:** “I didn’t know what a CRF [Case Report Form] was, but since I’m at the R-IDVT they trained me on this, and as I have been here from the undergrad, I learned it.” [Sub-Res, R-IDVI, KINGE, Nov-05-2014]

So, these two quotes show that this know-how and also conceptual knowledge was acquired in-situ, in the research group, being directly involved in a clinical project. This evidence illustrates how inexperienced staff benefit by working with experienced researchers and in environments where knowledge and information are exchanged continuously. Then, as has been highly discussed in the literature (Davenport, De Long, and Beers 1998; Nonaka, von Krogh, and Voelpel 2006), a common space for the interaction of team members with different degrees of experience allows the creation of a common language to interact and to understand the basic concepts. At these experienced sites, the constant interaction enabled new staff to learn the clinical trial terminology, such as what is a CRF, how to implement the protocol and the conceptual and scientific underpinnings of the project under execution. In this way, experienced staff in these academic groups become an important source of knowledge to close the

knowledge gap between inexperienced team members. Therefore, the active interaction between new and experienced staff enhances the learning process of newcomers and facilitates the acquisition of knowledge. It also expands the knowledge base, enhances knowledge sharing, promotes learning and improves organisational knowledge (Yan 2011).

However, in Colombia, the national regulations to implement clinical trials determine the composition of the research sites and therefore their knowledge-base. The Colombian regulation 2378 of 2008 on good clinical practices, unlike the other two country regulations (Brazil and Mexico), delimits the professional profiles of the personnel working in the laboratory processing the samples or handling the research product.<sup>29</sup> This fact influenced the configuration of the clinical teams and, therefore, the use of the previous knowledge that existed in the team working on the trial in Colombia. Specifically, the change in the regulation in Colombia directly affected the team configuration in the KINGE site, influencing the staff. The regulation 2378 of 2008 came into force in 2010 after a transition period (data provided by the regulatory agency), which reshaped the configuration of the research team (R-IDVT) between phase I (2008) and phase II (2012) trials as the next quote indicates:

“In the project in Rionegro [Colombia (Phase I)] the person that was doing it (preparation of the vaccine) was a microbiologist. Because the new norm required that this must be made by a pharmacist, I was hired.” [PQ R-IDVI, KINGE, Nov-06-2014]

Although the people interviewed did not mention that the regulation in Colombia influenced the performance of the team, the new regulation demanded an internal redistribution of responsibilities among the staff. This reallocation, according to Leonora Opalo (R-IDVT, Project manager), was “very, very hard” because they had to hire new people to fulfil the regulation. For example, because of the new regulation one

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<sup>29</sup>2378 resolution states that professionals assigned as responsible for research in the laboratory have to have an academic title of the next professions and a professional experience in clinical laboratories of at least two years: a) bacteriology b) microbiology c) chemistry or pharmaceutical chemistry, with training in one technical area of clinical laboratory d) medicine with specialisation in clinical pathology or a technical area of laboratory clinic, and personnel involved in blood samples and its processing, conservation and transport should be : a) bacteriology b) microbiology c) chemistry or pharmaceutical chemistry (Ministerio de la Protección Social 2008, 2008:78).

pharmacist had to be hired to manage the drugs and vaccines that were managed by a bacteriologist before, who could not use her experience in the new project and she had to transfer the lessons learned to the pharmaceutical chemistry.

Additionally, because of the regulation, the person that was working on Phase I handling the drugs had to be reallocated to new functions because she was not a chemical pharmacist, so this disturbed the team dynamic. In the case of SAVA, in Colombia, those that processed the blood samples were bacteriologists and microbiologists. Biologists, nurses and clinical technicians were not delegated with functions to take, process or transport on blood samples. However, in Mexico and Brazil, professionals in these three areas were predominantly part of the research site and worked on the project in the positions that the Colombian regulation impede. For this reason, in the SAVA case in Colombia, the professional composition of the research sites was different than in the other countries working for the same sponsor, so again the context, especially the regulatory one, shaped the knowledge-base of the site. This data reveals how a regulation that had the aim of standardising, in the country, the professionals that are part of a trial, reduced the employability of specific careers on these activities and also created variations among the knowledge-bases among sites working for the same project in different countries and disrupted the work dynamic in research teams already consolidated. As the case of Colombia showed, the regulation has a direct influence on the composition of the personnel working for the research. Also, although some staff in the organisation possess the knowledge to implement the procedure, only people authorised by the regulation to undertake a specific task can use it. Then, in Colombia's sites not only does it matter if personnel at the site have the experience to implement the task, having the right to use the knowledge possessed defines what of the knowledge-base residing in a firm is really employed to implement the project.

### 5.3.2. New research sites and the acquisition of knowledge by inexperienced staff

The acquisition of knowledge in the new research sites working for SAVA differed in some aspects with the acquisition of knowledge by new people working in academic groups working for NUSTAN and KINGE. In the new sites that worked for SAVA, only

one principal researcher (these are different to the key opinion leaders who were the SMO leaders) of seven interviewed had previous experience conducting clinical research. The rest of the personnel at these sites manifested that before the project they did not know *how to* execute the protocol following ethical principles for medical research, or how to work according to international standards such as the ICH-GCP, or didn't know the main concepts of clinical research. This gap in the knowledge demanded a learning effort to understand the project and especially its implementation.

In the academic context, researchers' names are equal to brands. Each name has associated reputation, value and power within the academic and medical community. Because of this, some sponsors try to recruit researchers with strong leadership in the fields so they have "the capacity and power to coordinate the study and can generate cooperation agreements between institutes and health state authorities" [SAVA Sponsor Mex, May-07-2015]. Once trials conclude, sponsors try to use the value associated with the name of the principal researchers and use it when they are commercialising products. As a person in SAVA said, they were interested in recruiting key opinion leaders:

"Because the key opinion leader will help you to sell the molecule, the good researcher that is dedicated to evaluating the patients because the key opinion leader does not have time. So, we need to search for key opinion leaders with a good research team and the researcher that is dedicated to the research." [SAVA-Sponsor Col, Mar-24-2015]

Under this logic, the sponsor first identified the key opinion leaders that would help to promote the vaccine results, and these leaders configured their own clinical teams and created a network of research teams to implement the projects. Then these key opinion leaders created temporary SMOs. The reason for this decision was that in the rural areas in Colombia and Mexico, where the sponsor required to implement the trial, research capabilities to execute the protocol did not exist. Then, these key opinion leaders and SAVA established an agreement. In most of the cases, SAVA provided the funding to create the research sites, and the key opinion leaders, through their organisations, created the research sites and trained staff. Only in one case, the key opinion leader in Colombia had a private SMO, so he created new branches where the sponsor required to implement the trial, and he evidenced potential to implement other trials with the

infrastructure created. The other research sites created by the SMOs in Colombia and Mexico were temporal groups of people working together for the first time, so they had to learn how to implement a clinical trial together.

The staff invited by the SMO (key opinion leader) to be on the project had to have at least some experience related to the tasks to implement the project. So, the SMO “selected personnel with experience with the infection although they did not have [experience] on research” [PI-SMO-3, SAVA-Mex, Jun-24-2015]. In this way, at least the principal researchers on the site had the medical knowledge about the disease, so with this knowledge they could build the rest of the concept required to conduct clinical research. Other site members like nurses, technicians or social workers also had specific knowledge about the task to implement for the project like vaccination procedures, medical evaluations or blood sample management. Employing this technical knowledge, the SMO expected that the staff could learn and link the rest of the conceptual knowledge about the project, the vaccine and the disease.

The SMOs and the CROs trained the sites theoretically in every aspect of clinical research, explaining the protocol and the Standard Operative Procedures (SOPs) of the project. The training received by the new sites is explained in the next quotes:

**Quote 1:** “There were meetings with all of us; we all received training, including researchers who did not have experience, then we received information from the sponsor. The coordination was by telephone, teleconference between all the researchers and direct supervision of the sites by SMOs.” [PI 2-Site2, SMO-3, SAVA-Mex, Jul-01-2015]

**Quote 2:** “There were around 10-12 meetings, we had training on the protocol, participant recruitment.” [PI-Site3, SMO-3, SAVA-Mex, Jul-08-2015]

**Quote 3:** “To be part of the project we had to present a series of evaluations, and we had the online training to pass the exams. We had conferences, and we were going and coming [reference to another site]. Then, we presented the exams, and it defined those that would be part of the site.” [LT-Site-4, SMO-3, SAVA-Mex, Jul-09-2015]

**Quote 4:** “Everybody had to be [at the meeting], so everybody could understand what they had to do, about what was the protocol, what was the process order.” [OM SMO-2, SAVA-Col, Dic-03-2014]

As the quotes indicate, this training allowed for the personnel at the site to acquire the conceptual basis to implement the project. As quote 3 clearly points out, only the staff

that displayed, through an exam that they had to learn the concepts associated with the project and procedures to implement were invited to be part of the sites.

However, although the exams were a method to identify if the staff had acquired the knowledge to understand and implement the project, for the sponsor, it was a considerable risk to initiate the vaccine trial with inexperienced staff that did not know how to implement the project. For this reason, one of the SMOs in Colombia proposed the execution of a pre-trial to collect data to identify the serotype circulation<sup>30</sup> in the studied population. This trial had the primary objective to train the staff in practice to close this knowledge gap and level, in all sites, (Colombia, Brazil and Mexico) their knowledge before initiating the vaccine trial. The pre-trial implementation sets the basis for a new method to create knowledge in inexperienced research sites, which so far is a unique case in the pharmaceutical industry.

The pre-trial consisted of a Prospective Cohort Study with Active Surveillance for the disease in a population of 3,000 children between 9–16 years of age (Dayan et al. 2015) for ten months. However, the fact that the staff did not have previous experience doing clinical research made the acquisition of knowledge difficult, as the next quotes illustrate:

**Quote 1:** “At that time, we didn’t have the concept or the vision of doing research. It was a bit complicated because it was a learning process, and still [it is]. I think that research is a continuous learning [...], but it was complicated but interesting.” [Underline added PI-Site-1, SMO-1, SAVA-Col, Dic-10-2014]

**Quote 2:** “At the beginning of the trial, the team does not have the experience to know the procedure, how many the [procedures] are, where to do it, where not to do it, then at the beginning [deviations] are very recurrent regarding procedures.” [Monitor-CRO, SAVA-Mex, Jul-08-2015]

**Quote 3:** “Many did not have the experience in clinical research, they find it hard, we gave the training, and little by little all of them acquired [the knowledge] without a problem.” [PI 2-Site2, SMO-3, SAVA-Mex, Jul-01-2015]

So, as these quotes indicate, because staff did not have the background and the knowledge required to implement the protocol, they struggled to learn the concepts and how to proceed. Moreover, the first quote points out that although the personnel

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<sup>30</sup> With this data it was possible to define which specific viruses’ serotypes were present in the population at that time and which serotypes the population had had contact with in the past.

reached a level of understanding about clinical research, the learning process was demanding and gradual, as the third quote also indicates. Therefore, the cognitive distance (Nooteboom et al. 2007, 1017) between the knowledge possessed and the knowledge that they had to acquire staff at the new site demanded a strong learning effort to learn the practical and conceptual knowledge to implement the project and follow up the multiple requirements of a clinical trial.

Some SMOs expressed that, many times, teams considered that they had understood the procedure and implemented the activities, but unfortunately, they were having problems with the implementation. A high number of deviations reported in the pre-trial and at the beginning of the project indicates the struggle lived by the sites to implement the protocol according to the ICH as monitors, the sponsor and one principal site researcher stated:

**Quote 1:** “Question: at the beginning, in which areas did you have deviations?

Answer: Almost in all areas, they did not document the process, or they left the time pass to call people, they did not take note about the date of the visit, or the date in which the sample was collected. These kind of details.” [PI-Site3, SMO-3, SAVA-Mex, Jul-08-2015]

**Quote 2:** “The deviations depend on the stage of development of the study. In the beginning, the team does not have the experience about the procedures, how many are, when to do it, when not to do them. So, at the beginning, deviations were recurrent on procedures. As the study progresses, if there are not big amendments and if the team is well trained, the deviations are not repeated.” [Monitor-CRO, SAVA-Mex, Jul-08-2015]

**Quote 3:** “All of them understood, but over the practice, they thought that was not necessary [to collect] so much information, then they stopped to do it [data collection], and we asked, why didn’t you do it? [Answer] ‘I thought it was not [necessary].’ [PI 2-Site2, SMO-3, SAVA-Mex, Jul-01-2015]

So, as these quotes indicate and the evidence presented in this sub-section reveals, over the implementation of the task, personnel not only had to learn and understand the information transferred initially by the sponsor and the SMO. This knowledge also had to be used to produce the data following the instructions provided, and this was highly demanding because they interpreted the instructions in multiple ways that did not correspond to the procedures indicated. The reason behind this was the lack of know-



how to properly implement the instruction and also the lack of a constant example in the research site from whom to learn the procedures to implement.

Personnel at the research site were in contact with the SMOs' directors (key opinion leaders) through email and phone calls. However, these experienced researchers were not present in the actual implementation of the activities in the sites, so the know-how to implement the project was transferred through instructions rather than with real examples, as is illustrated in the next quotes:

**Quote 1:** "The monitoring team was not there all time. The coordinator (SMO) is the one that had to be in contact day by day with the site. Then, the objective was to create that relationship, a link, the closest possible, in this way, if the site had doubts it consulted immediately." [SAVA Sponsor Mex, May-07-2015]

**Quote 2:** "Then, the sites had taken that awareness. The people already know, and they call me. [Site]: 'It has emerged this, what do we do?' Sometimes I don't know, so I have to ask the doctor [SMO], if he doesn't know, then, we ask the sponsor, so this is a chain. The objective is to do the things right, and everybody knows that they cannot act without asking." [PM-SMO-1, SMO-1, SAVA-Col, Dic-10-2014]

**Quote 3:** "When there were things that we did not understand, they give us teleconferences, then, they explained to us what it was about." [NRS-Site-4, SMO-3, SAVA-Mex, Jul-09-2015]

Because the SMOs and the researcher sites were in different locations, the staff at the site who had any doubts had to consult the SMOs via email or phone calls. Personnel from the SMO constantly travelled to the sites to provide advice, but they were not there working in the sites, teaching how to do the activities. However, they did not have a person *in situ* teaching them with examples of how to implement the projects. Only after the results were obtained, through monitoring, was it possible to identify if sites implemented the protocol according to instructions imparted, the ICH and SOPs, and if personnel really had learned. One example of this evaluation is this quote: "The monitor comes and review the files; she reviews if it is good or not and then she explains how it should be." [NRS-Site-4, SMO-3, SAVA-Mex, Jul-09-2015] Then for the sites, learning how to implement a clinical trial consisted of a process of trial and error with feedback loops, which was demanding and time-consuming.

As a result of this pre-trial, staff members expressed how they learned how to execute a clinical project, including: how the relationship should be with the monitors; how to

introduce the GCP into their professional practices; how to conduct an informed consent; how to obtain and send blood samples; how to follow and report adverse events to the ethics committees and regulatory authorities; what contracts and agreements they had to create with the hospitals to access information and how to interact with the community. Expressions like:

**Quote 1:** “I think that without it (pre-trial), we could not have made the trial.” [Luz Elena Nuñez project manager SAVA Site1- Col]

**Quote 2:** “It was a free university... we learn the practice and the theory together.” [PI-Site-1, SMO-1, SAVA-Col, Dic-10-2014]

And

**Quote 3:** “Yes, it was a learning for all of us, it was the way to get involved early and in a calm way to the study. The study was calm with few subjects, so it was a very good strategy.” [PI 2-Site2, SMO-3, SAVA-Mex, Jul-01-2015];

reflect the relevance that this pre-trial had for the learning of new knowledge. In this way, this pre-trial allowed them to implement, in a real project, the concepts acquired over the training provided by the SMOs. In the end, those that acquired the knowledge to implement the trial were invited to be part of the vaccine clinical trial as this quote from the paper published with the pre-trial results indicates:

“The teams at all sites showed their ability to capture and follow up acute febrile episodes within the timeframe specified in the protocol to confirm symptomatic dengue cases, which confirmed the feasibility of implementing an active surveillance system to detect and diagnose symptomatic dengue cases in multiple countries in Latin America.” (Dayan et al. 2015, 22)

With the execution of this pre-trial, the sponsor decreased the risk of implementing a trial in sites without the experience where mistakes would cost the project’s success.

In the literature, it has been discussed which approach is better to learn know-how, if learning from experience or learning from example (Pentland 1995). Based on the cases of SAVA, NUSTAN and KINGE, I argue that in the case of clinical research, learning from example enables the acquisition of know-how in a less traumatic way compared with the evidence presented by SAVA. In SAVA sites, the trial and error process lived by the research sites was demanding and it required long cycles of feedback loops. Although SAVA implemented a pre-trial where this learning by doing took place, in a

clinical trial the implementation of procedures wrongly has direct consequence for the data quality as it was present and therefore on the final results. Then in the context of clinical research and the training of new staff, sites without additional experience of learning by doing need a physical accompaniment that provides the example and guidance on how to proceed. Moreover, it has been found that the more interaction with experienced staff, the more information is learned (Park, Im, and Kim 2011) where training might involve, in the long-term, transferring personnel to the provider's location (Roy and Sivakumar 2012). Therefore, if there is not a rule that impedes the presence of the trainers on the execution of the project, experienced staff should have responsibilities delegated in the sites and execute initial parts of the project with the personnel until they learn the fundamentals of the procedures. The acquisition of know-how requires constant interaction and learning from example.

As was mentioned, researchers with previous experience in research working for the NUSTAN and KINGE sites manifested that the process to collect data was routine because they already know the procedures and how to write good medical notes. Young physicians working for NUSTAN, KINGE and SAVA sites participating for the first time in a clinical trial found the procedures easy to follow and logical; for them, it was not complicated to introduce the GCP and the procedures indicated in the protocol into their medical practices. This openness to learning is explained by the fact that they had not developed a consolidated work routine that they had to reshape, so the acquisition and integration of this know-how were simple. In contrast, physicians working for SAVA who had substantial clinical experience, but did not have a research background, found it complex to include the GCP into their medical practice, as the next quotes illustrate:

**Quote 1:** “The project required a personal and professional re-engineering, this had some difficulties, it is much easier if you are trained since the beginning compared if you need to straight up yourself on the road, that happened to me.” [PI-Site-1, SMO-1, SAVA-Col, Dic-10-2014]

**Quote 2:** “You need to teach people, the resistance to change ‘hijole’ it is one of the biggest problems that you are going to see everywhere.” [PI-Site3, SMO-3, SAVA-Mex, Jul-08-2015]

**Quote 3:** “This way of collecting the data and be attached to the norm, it is not easy, sometimes you forget a point, and they call you, ‘you forgot to write this’. Sometimes, I feel that some things do not affect so much, but maybe they do, so we

try to follow the project, avoiding deviations, doing the things correctly, the truth is that it is hard, at least for me that is the first time.” [Sub-Res-Site 4, SMO-3, SAVA-Mex, Jul-09-2015]

Then, as these quotes indicate, having rooted know-how, rather than enabling the acquisition of new ways to implement a task and learning new procedures, it obstructs this acquisition of this new knowledge. The proof is that young researchers with fewer experiences manifested that learning new procedures was easy for them compared with highly experienced researchers, as the ones quoted above. This difficulty in adopting the operative procedures and following the GCP by the staff has also been reported in other vaccine clinical trials in Asia and Africa, where periodic monitoring visits by CROs – not coordinators – were necessary to insist on complying with SOPs (Acosta et al. 2007; Geldenhuys et al. 2012). This evidence reflects an early resistance of researchers to adopt the practices and follow up the procedures of the project. These findings of the acquisition of new know-how are consistent with the argument raised by Ottevanger et al. (2003) who stated that the harmonisation of routines among physicians could be difficult because physicians that are not familiar with these routines face more challenges to acquire them in practice. But also, these findings reveal that previous experiences can be an obstacle to learn new practical knowledge, as Cook and Brown (1999) suggest. They stated that: “Many people experience a period when explicit knowledge about how to move one’s feet or hold one’s shoulders can actually impair one’s ability to acquire the tacit knowledge necessary to perform the skill in a fluid or masterful way.” (Cook and Brown 1999) Acquiring know-how takes longer, especially where their previous knowledge is profoundly rooted.

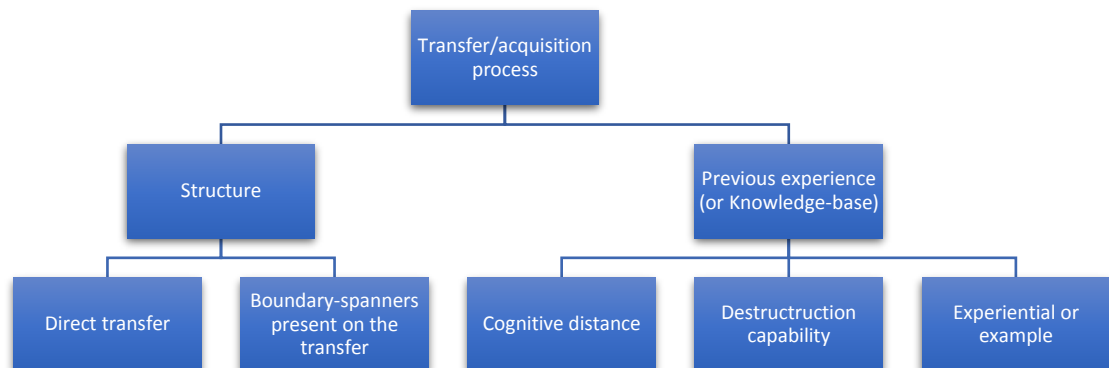
In conclusion, the evidence presented indicates the relevance of the knowledge-base of the people working on the project on the acquisition of knowledge. The analysis of the knowledge-base and its influence on the acquisition of knowledge requires a distinction between conceptual knowledge (know-what) and practical knowledge (know-how), as the data indicates. In the three cases studied, mainly all people interviewed had the conceptual base to learn about the disease and the clinical trial; physicians, lab managers, nurses, data managers had a profession related to the activity to be undertaken. Using this knowledge, people build the *theoretical knowledge* about the project. In contrast, only those that had previously worked in clinical research had the *know-how* to understand how to implement the procedures according to the protocol,

as was the case of some of the personnel working on the NUSTAN and KINGE sites. As it was presented, the environment and the constant interaction with experienced people influenced the acquisition of the know-how. In academic research sites, experienced and less experienced staff cohabited, where these last ones could learn from experienced personnel because of the constant interaction that took place at the research site. In contrast, in new sites managed by the SMOs, personnel in the research sites interacted less with experienced researchers, so the acquisition of the know-how was slow. Also, the data presented reveal that having a practical knowledge-base associated with the knowledge that must be acquired not always enables the acquisition of new know-how. Physicians with long experience as a general practitioner (but not on research) were reluctant to acquire and integrate the new know-how into their medical practices compared with young researchers, who had less rooted know-how and, therefore, were more flexible in learning new procedures to conduct a medical consultation. Then, this differentiation between practical knowledge and conceptual knowledge lets us better understand the relevance of previous knowledge in the acquisition of knowledge, leading me to argue that only previous conceptual knowledge allows the building of new concepts and, in contrast, previous practical knowledge can be a factor that decreases the ability to acquire new know-how. Then, practical and conceptual knowledge-bases cannot be considered the same on the analysis of the relevance of the knowledge-base in the acquisition of knowledge.

## 5.4. Conclusion

This chapter meant to answer the research question: ***To what extent does the structure designed by the sponsor to transfer knowledge, the permeability of the research sites, and the previous experience of people working on the project influence the acquisition of knowledge in the research sites?*** The evidence presented indicates that in interdependent activities that take place in multi-organisational projects, these three factors directly influence the acquisition of knowledge by the staff working in the research sites. These factors defined what knowledge and information the personnel received, and affected the disposition and capability to receive, understand and implement the transferred knowledge. A summary of the three factors and levels of analysis are summarized in Figure 7.

**Figure 7. Summary of factors influencing the transfer/acquisition of knowledge between the sponsor and the research sites.**



In the first section of this chapter, I discussed the influence of the structure designed by the sponsor on the acquisition of knowledge or information by the personnel working on the research sites (Figure 7). The data presented showed how a direct communication between the sponsor and the site's staff has a positive effect on the acquisition of knowledge by the personnel, ensuring that sites receive all the information needed to execute the project. In contrast, structures to transfer knowledge and information that had the presence of intermediary actors/boundary spanners (CROs, SMOs) showed to be less efficient, slowing down the communication between the parts, creating gaps in the transfer of information or blocking the acquisition of information to the sites. The fragmented structure within the CRO to transfer the information across multiple personnel working in the trial decreased the speed in the communication, and in some cases impeded the flow of information from the sponsor to the sites. Regarding this point, I presented how the presence of experienced staff decreased the risk of loss of information over the transfer because they knew what to expect and, therefore, requested that. So, the knowledge of the

personnel at the site is vital to overcoming the slow flow of information or the gaps that could emerge.

A structure with multiple intermediaries, rather than providing continuous support to the sites and enabling the acquisition of knowledge, created fragmentations in the transfer of information and confusion in the sites. The evidence also indicates that as the number of intermediary actors increases, the acquisition of knowledge is affected, and sites start to develop a high permeability for one of the sources. This permeability at the end defines which knowledge is acquired and which is not by the sites. So, in this way permeability also influenced the acquisition of knowledge and information. Trust in sources was reported as a key factor mediating the permeability of the staff towards external sources, and this trust depended to a large extent on the experience of the person transferring the information. Personnel at the site easily accepted information communicated by the SMOs or experienced CROs rather than novice CROs. Another element discussed was the permeability of the research sites. The permeability of the teams towards a source is not static, so this one can shift from open to closed or vice-versa, according to how the personal relationship and trust among parts evolve over the course of the project. Then, this evidence contributes to the discussion about the concept of permeability developed in this thesis.

In the last section of this chapter, I discussed how the experience of the personnel working in the research sites influenced the acquisition of knowledge to implement the clinical trial. In the research sites, the staff had the professional background which provided the conceptual bases from which they could build the concepts required to understand the project. However, the level of previous experience doing clinical research directly influenced the acquisition and use of the concepts acquired over the initial training. As the NUSTAN and KINGE cases show, in these sites personnel had the knowledge bases to understand the project and implement it. Also within these sites, personnel without previous research experience learned directly from their colleagues the bases to implement the project, so learning from example was relevant. One of the findings in this chapter is the role of the regulatory agencies determining the professionals that can work on a clinical trial, which conditions the knowledge-base of the site. The SAVA case shows how a low level of previous experience slows down the acquisition of knowledge and its implementation, but most importantly, this case

shows how personnel with vast experience on related activities were reluctant to learn new know-how to implement clinical research. This situation is explained by the fact that to acquire new practical knowledge people must modify, replace or reshape the old knowledge to introduce the new practical knowledge, which demands a tremendous effort. Therefore, this evidence indicates that previous practical knowledge or similar activities, rather than enabling the acquisition of new practical knowledge, can create an obstacle for it. Then, the next step to continue studying the flow of knowledge in multi-organisational projects is to understand how the knowledge acquired was employed in the research sites to produce the clinical data.



# Chapter 6: Opening the black box of the research sites. Implementation of the protocol and clinical data production

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## 6.1. Introduction

Previous studies about knowledge management in the pharmaceutical industry have been limited to the relationship between the pharmaceutical company and the CROs (S. Gupta and Polonsky 2014), the hierarchies in the transfer of knowledge and knowledge creation between CROs and the pharmaceutical (Azoulay 2004) and the risk of losing knowledge by the pharmaceutical company and their dependency on external suppliers (S. Gupta et al. 2009). However, practitioners in the industry have broadly discussed the work and contributions of the research sites and this topic has been less addressed in the literature of management. This chapter aims to address this gap.

Using the model proposed in Chapter 2 to study the flow of knowledge across organisations and its use within the firm, in the last chapter, I discussed in depth the acquisition of knowledge, data and information from the research sites working on the three case studies. This chapter addresses the other two steps of the model at the intra-organisational level. The use of the knowledge to solve productive inquiries and evaluate the results, and the storage and transfer of results to an interdependent organisation requiring this information to conduct their work. In this way, this chapter provides an answer to the third research question of this project, which is: ***How is knowledge employed in the clinical research sites to solve the productive enquiries related to the production of clinical data and transfer the results to the sponsor?***

As it was proposed in the conceptual model in Chapter 2, at the use phase organisations create their knowledge products and these products are stored and shared in different formats with other organisations (M. H. Meyer and Zack 1996). In this phase,

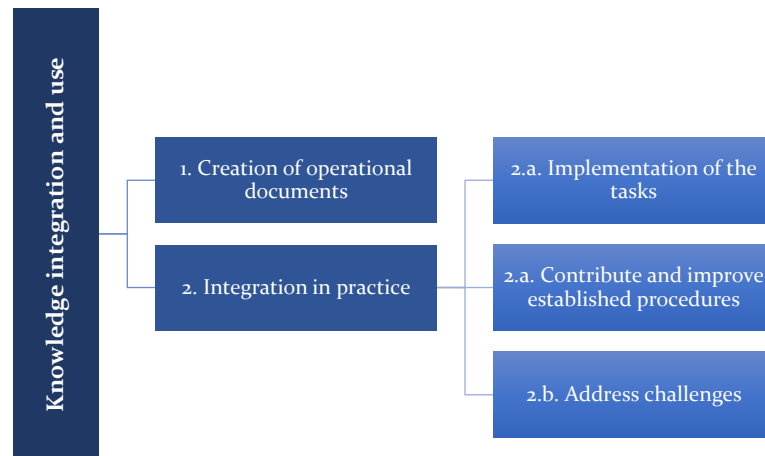
knowledge is employed to analyse and integrate information to the organisations, and standardise procedures (Evans, Dalkir, and Bidian 2014). This chapter separately addresses the production of clinical data from the transfer of results to answer this research question. In this way, this chapter is divided into three sections. In the first section, I discuss the integration and use of knowledge within the research site. For this, I address the operationalisation of the knowledge acquired through the creation of the standardisation of procedures within the research site, the use of knowledge in practice to recruit volunteers for the project, to produce the clinical data and contribute to the protocol implementation. In this section, I explain how physicians used their medical knowledge, about the disease and the project, and the information gathered from volunteers to produce the clinical data. This section is central because physicians are the ones that capitalise all the previous effort to design, training, standardisation and recruitment in the diagnosis of the infection; this means the production of clinical data. Also, I discuss the relevance of knowing how to produce the clinical data according to the standards of the industry and the sponsor to ensure the quality and validity of the clinical data collected. It is in this section that I analyse the integration of knowledge in the activities of the research sites to implement the protocol in which the 'epistemology of possession' and the 'epistemology of practice' (Cook and Brown 1999) converge in the execution of the task.

The second section discusses the learning loops that took place over the course of the trial and their relevance to improving the staff performance. The third section addresses the transfer of clinical data to the sponsor and the strategies designed by research sites to ensure participants' adherence to the project using the integration framework proposed by Anderson and Parker (2013). Also, because of the frequent turnover of personnel in the research sites, I discuss the relevance of storing the lessons learned over the course of the trial. In conclusion, this chapter aims to explain the use of knowledge in the implementation of the clinical trials in each one of the steps, where not only the medical knowledge of physicians was essential, but also the work and knowledge of other staff members were crucial to the project success.

## 6.2. Integration and use of knowledge within the research sites

In outsourced projects contractors need to integrate the knowledge received with their local knowledge and operationalise it to create the product demanded (Jackson and Klobas 2008). In this process, the outsourced organisation develops new organisational capabilities to manage all knowledge and information: the old one, the one received and the new one, when the capabilities are oriented to learn, apply, merge, create, record and transfer the knowledge (Dalkir 2005). In a clinical trial, sites integrate the acquired knowledge constantly into their knowledge-base and create the capabilities to implement the project.

**Figure 8. Mechanism to integrate knowledge in the organisation and address the productive enquiries.**



In the first section, this integration process is addressed (Figure 8). Here it is argued that integration was not linear and in some cases the integration gave explicit documents as a result; in other cases, outcomes consisted of the actions of other people. In this dynamic process of integration and use, in this thesis two mechanisms to integrate knowledge and use it were identified. The first mechanism was the standardisation of procedures through the SOPs manual (Figure 8-1). In this process, each site integrated the knowledge received with their knowledge of their local dynamics, the regulation and the community to define how to operationalise the protocol. The second mechanism is the actual use of the acquired knowledge in

standardised activities (Figure 8-2.). In this scenario, personnel in the sites used the knowledge directly to produce the clinical data (Figure 8-2.a), to present alternatives to optimise the strategies proposed by the sponsor (Figure 8-2.a) or to overcome the challenges associated with the implementation and recruitment of participants (Figure 8-2.b). In this way, the knowledge, information and data acquired are employed to execute the activities, and produce the knowledge products (M. H. Meyer and Zack 1996), give a solution to problems (McElroy 1999) or, as it will be presented, to contribute with alternative proposals. Below I address each one of the two mechanisms to integrate knowledge and its associated activities.

### 6.2.1. The creation of operational documents

In international projects the standardisation of the protocol and procedures among participants is a challenging activity because of the variation in practices among organisations (Sprague, Matta, and Bhandari 2009). In addition, the integration of the knowledge acquired into the organisation requires its operationalisation (Jackson and Klobas 2008) and integration into daily routines (Maier 2004). One effective and efficient mechanism to integrate knowledge and standardise procedures is the creation of standard operating procedures to ensure consistency of actions of individuals within organisations helping to coordinate clusters of actions and drive decision -making (McIver et al. 2012).

In the clinical trials, one way to operationalise this knowledge is standardising the procedures indicated in the protocol. For this, each research site must create Standard Operating Procedures (SOPs) manuals. The SOPs definition is: “detailed, written instructions to achieve uniformity of the performance of a specific function” (ICH Harmonised Tripartite Guideline 1996, 8). These documents have the step-by-step of each procedure and the delegated responsibilities of each staff member according to the protocol. As one project manager indicated, these SOPs must be very specific, and clear so that “if a person must make the process and does not have instructions, with that [SOP] he can reproduce the process” [PM R-IDVI, KINGE, Nov-05-2014]. The SOPs are exclusive for each protocol. One clear example of this is that although the research site R-IDVT executed the clinical trial Phase I and Phase II for KINGE, they could not employ the SOPs designed for Phase I on Phase II. The research site had to “modify the

SOPs for the Phase II” [PM R-IDVI, KINGE, Nov-05-2014]. Then, the knowledge and information acquired about the project are transformed in detailed procedures consigned in the SOPs manuals, which guide the actions of people working on the project. This fact clearly indicates the degree of relevance of SOPs for governing the actions of the personnel participating in the clinical trial and setting up the day-to-day activities and indicating how staff must perform procedures.

The process to integrate the acquired knowledge and the knowledge of the site to create the SOPs differed in the three cases studied. However, the conceptual bases and information and knowledge employed to create the SOPs were similar among cases. In the first place, the person to create the SOPs had to use her/his knowledge to adapt the procedures indicated in the protocol and the manuals transferred by the sponsor to the context of the research site and the local regulation, as the next quotes indicate for the different cases:

**Quote 1:** “The protocol establishes clearly the clinical aspects. Then, you don’t have to invent anything. You have to take the protocol to create the manuals; you can create a unique operational manual including the clinical follow up. In our case I did the manual for the Morelo sites, we evaluated it and then we shared it with the other sites.” [PI-SMO-3, SAVA-Mex, Jun-24-2015]

**Quote 2:** “The SOPs are building with the study coordinator, because [it] depends on the structure that you have, [it] depends on the team. So, we could not borrow one SOP or flow chart, not, it is impossible because we have differences between institutions.” [PM-USP, NUSTAN, Apr-01-2015]

**Quote 3:** “They [Morelos team] send us a guideline, but each one had to adapt them to its unit, to the culture, to the operations. It is not the same in Temizco that they have 1000 and more [participants] than us that we have the half.” [PI-Site 4, SMO-3, SAVA-Mex, Jul-09-2015]

**Quote 4:** “Each site has its manual, each one with its particularities because any SOP works for all. That would be a big mistake; we had to individualise it [manual] because each site has different characteristics.” [PI- R-IDVI, KINGE, Oct-15-2014]

**Quote 5:** “The informed consent process is not the same in all parts of the world. Then, you need to adjust it [procedure] depending on the country and the site.” [SAVA Sponsor, Col, Mar-24-2015]

In the first place, as quote 1 indicates, the manuals were designed based on the protocol. The person responsible had to use the knowledge acquired previously about the protocol and had to complement this knowledge with his/her knowledge about the

team (quotes 2-4), the culture of the communities (quote 3) (i.e. what activities can be implemented to contact people and to recruit them) and local regulation (quote 5). For example, among countries, there existed differences in the procedures to sign the informed consent. For this reason, the sites in Colombia and Mexico had to adapt the process indicated in the protocol to the requirements of the country, such as the number of identification copies to obtain and the signing of the informed consent by two parts. Therefore, the person responsible for creating the SOPs to operationalise the protocol in executable tasks needed to know the protocol, the requirements of the local regulation, the technical procedures required to execute the project, and the team members' responsibilities. In this way, multiple pieces of knowledge that are complementary are brought together and externalised in one consistent document to be shared with the rest of the personnel, as Landry et al. (2006) also suggest. It is in the standardisation of procedures that the protocol reaches its full potential as a boundary object (Star and Griesemer 1989), being plastic enough to be adapted to the site dynamics, work practices and local regulation, conserving its essence across sites over the standardisation of procedures.

In most of the research sites and SMOs, one person created the manuals, which evidences how the vision of one person about how the protocol should be implemented prevails in this standardisation process. The person who creates the SOPs using this knowledge made explicit his or her mental model about how procedures should be implemented, unifying practical criteria around the trial (Maier 2004). In the cases of KINGE and NUSTAN, the vision of the project manager in the sites was the one that defined the actions in the SOPs. In both cases, the project manager had better knowledge about the process to implement procedures compared with the principal research, which was usually absent from the physical site space. In the cases of SAVA, the principal researchers working for the SMO-1 (Colombia) and SMO-3 (Mexico) were the ones that added the modified initial version of the SOPs to their sites, adapting the protocol to their local contingencies. In the case of the private SMO in Colombia, the operational manager created the SOPs for each one of their research sites.

The SAVA case evidences two different degrees of control of the SMOs over the research site, modulating the contribution or not of the site's personnel to the standardisation. In Colombia, all the sites managed by the SMO-2 belonged to the

company, so the control of this SMO over these sites was direct and strong. The operations manager designed the manuals and trained the sites, giving small room for local researchers to contribute to this activity. In contrast, the sites managed by the SMO-1 (Colombia) and SMO-3 (Mexico) did not belong to the SMO. Sites were created and managed by the SMO, and almost all sites had independent teams configured by local hospitals only for the clinical trial. The control established by these two SMO was flexible and gave authority and control to the local researchers to adjust the SOPs to their local dynamics; even though being new research sites. The principal researcher in each site working for the SMO-1 (Colombia) and SMO-3 (Mexico) modified initial version of the SOPs (Quote 3), adapting the protocol and procedures to their local contingencies. Therefore, the SAVA case provides a new light about how standardising activities take place in research sites managed by SMOs; a rising figure in the clinical trial industry, and the control that SMOs manager exercise on the research sites.

In summary, the data presented for the three cases elucidates how one person dominates the integration of knowledge into the site routines, either the project manager or the principal researcher in the research site, or the operations manager in a private company. In most of the cases, the manager or principal researcher shared the SOPs with the staff members to learn and understand the action, creating, in turn, a shared understanding of how they should follow the procedures over the course of the project and extending his/her vision about the task and the protocol. It was through the socialisation of these SOPs that protocol procedures, once adopted by people, are institutionalised into the standard routines of the research site (Bruni, Gherardi, and Parolin 2007).

However, the creation of the SOPs and its implementation in the sites does not mean a full standardisation of procedures. Some key opinion leaders in the SAVA case suggested that regulatory authorities or the sponsor should evaluate the manuals created by the sites before initiating the project. For one of these researchers:

“It was a mistake that manuals were requested only once you concluded the active phase and you initiated the hospitality phase; this should be since the beginning, this is a mistake from the laboratory and the principal researcher.” [PI 1-Site2, SMO-3, SAVA-Mex, May-15-2015]

Then, although sites created manuals at the beginning of the project, a validation of the coordinating firm is desired to ensure a correct standardisation. Then it is not only relevant to create the manuals according to the protocol, but it is also essential to verify if the SOPs addressed the procedures correctly. In this manner, it is possible to verify if the knowledge acquired about the project is integrated into the organisation properly through the creation of manuals that have to be followed by the rest of the team. In the literature, concerns have been realised about the strong standardisation of knowledge process, as this can decrease the importance of tacit knowledge in practice and people's capability to generate ideas and contribute to the project (Maier 2004; McIver et al. 2012). This concern is totally valid; however, the data collected indicates that high control of the routines through the standards and a central managerial organisation are the factors that reduce the opportunities for staff to contribute to the project. In those cases where personnel had more freedom to propose, they could contribute to the project and the process implementation, as will be discussed in the section 6.2.2.2. In addition, the implementation of activities such as the clinical evaluation of participants demands the use of the tacit knowledge of physicians and their medical expertise to provide the diagnosis. Then, although the SOPs standardise some activities, the implementation of these tasks gives room for the personnel to contribute and reflect, as I will present in the next sub-section.

### 6.2.2. Use of knowledge to implement the project activities

As the introduction of this section presented, the other mechanism to integrate acquired knowledge into the project activities is applying the knowledge possessed (Dalkir 2005), giving a solution to problems (McElroy 1999). In all cases, the creation of the SOPs was the first step to integrate the knowledge into the organisations; however, all the procedures indicated in the guidelines had to be executed to recruit, follow up and evaluate participants to obtain the data. Then in this section I address the actions and how knowledge was implemented to execute critical activities of the protocol, how local researchers, using their knowledge, contributed to improving the procedures indicated in the guidelines and addressed the challenges that emerged over the trial.



### 6.2.2.1. Implementation of tasks

One of the key activities in a clinical trial is the recruitment of participants. In this activity the staff are required to actively use the knowledge about the project to explain the project to potential volunteers. A key moment is the signing of the informed consent: without volunteers there is no project. In this activity the transfer must be clear to ensure that through the informed consent process, volunteers understand the project, their rights and responsibilities. This transfer is vital for the project because the informed consent is an ethical requirement and the legal contract between the principal researcher and the volunteer. Once volunteers sign the informed consent they have officially entered the clinical study as a subject<sup>31</sup> and they declare that they understand their role as a “subject of research”, their rights, benefits and even responsibilities (Nijhawan et al. 2013; Robertson and Gan 2001). For this reason, the signing of the informed consent by volunteers is considered one of the most critical activities in the execution of a clinical trial.

As the ICH-GCP indicated, personnel delegated in the site, and the physicians, had to explain the project carefully to the participants, resolve their doubts and give them enough time to review the information to decide if they wanted to participate in the trial, as the next quotes show:

**Quote 1:** “We, for example, read with them the informed consent, with the parents, the subject. We read everything, and we explain all, there are documents with 10, 11 pages. Sometimes people felt sleepy; they do not understand, so you need to ensure that they understand what I read, for me, it is the most complicated process.” [PM-Site-1, SMO-1, SAVA-Col, Dic-10-2014]

**Quote 2:** “We need to provide to them the [informed] consent to read, the assent, we give time. Then, they pass to me, and I answer all doubts, we ask them if they want or not to participate, and all that procedure corresponds to me.” [Sub-Res, Site2, SMO-3, SAVA-Mex, May-15-2015]

**Quote 3:** “Before the patient signs the consent, I need to be sure that he has really understood, that he is willing, that there are no interests in between.” [Sub-Res, R-IDVI, KINGE, Nov-05-2014]

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<sup>31</sup> “Prior to a subject’s participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion.”(ICH Harmonised Tripartite Guideline 1996, 15)

**Quote 4:** “The people vaccinating speak Maya. Although the woman come and she was illiterate, or she did not speak Spanish, she always was with her kids, husband or someone and we explained the project.” [Nurse-Site4, SMO-3, SAVA-Mex, Jul-09-2015]

So, as these quotes indicate, personnel at the site and, in particular, physicians had to use their knowledge about the project to explain it to volunteers, families and witnesses, including their rights benefits and responsibilities. The community-recruited mostly did not have the theoretical knowledge-base to understand the technicalities of the project. Then, the person explaining the informed consent had to develop skills to explain the project in a non-technical language without affecting the message and identify if the personnel had comprehended the project. This activity reveals the deep understanding that they had about the project and the disease, and analytical process that staff performed to transform and link technical concepts to daily life language to transfer the information, even in a different language such as Maya, as quote 4 indicates. In this way, through the project socialisation with volunteers (Nonaka 1994), personnel in the site displayed competence about the project, and used their knowledge in practice showing integration and appropriation of the project to socialise it with the community to achieve one of the most critical steps in the clinical trial, the subjects' recruitment.

Another key task in implementing the clinical trial is the production of clinical data. In this activity all previous efforts implemented by the site staff are summarised. Physicians are the only ones that implement this activity, who evaluate the medical condition of volunteers. Each protocol establishes the number of visits of the participant to the site and the variables that physicians need to investigate. In this activity, physicians had to evaluate the participants and identify if the participant had experienced any symptom associated with the disease under investigation. It is relevant to point out that physicians were autonomous in their diagnosis and they were not questioned about their medical conclusion, as Dr Macias indicated: “We have not had the case where a diagnosis is called into question.” (PI-Site 4, Mexico) Then, despite the standardisation of procedures, in the privacy of the interaction between physicians-volunteers, physicians had the freedom to use their knowledge to provide their diagnosis.

In the process to integrate the acquired knowledge into the medical practice, physicians narrated that in the three cases, they had to know the procedures indicated in the protocol for each visit, so they could collect the data required by the sponsor, as the next quotes for each one of the cases indicate:

**Quote 1:** “My work here has been examining the participants those days that are stipulated in the protocol and meet each one of the points indicated for each one of the visits.” [Sub-Res-Site2, SMO-3, SAVA-Mex, May-15-2015]

**Quote 2:** “At the point that the person receives the vaccine, we have to consider all the adverse events [that the] vaccine [is] responsible [for]. So we fulfil the term of adverse events, and then after the research or the clinical research or the laboratory results, we define if it was related to the vaccine or not related to the vaccine.” [Sub-Res-USP, NUSTAN, Apr-14-2015]

**Quote 3:** “[Disease] is a febrile illness. The first thing is to discard if they had had dengue; any type of fever, since dengue goes from nothing to severe symptoms. Then, we emphasise on it, if they have had fevers at each visit. Then, I do the control of the patients every time they come, that they did not have adverse events, and I do the monitoring and follow-up that is typically done with a vaccine.” [Sub-Res, R-IDVI, KINGE, Nov-05-2014]

As quote 1 points out, the researcher or sub-researcher following the instructions in the protocol knew what procedures to implement to collect the data in each one of the visits. Quote 3 presents an example of the process to produce the data, which shows that data production was not a mechanical action. This evidence contradicts some papers and guidelines that have suggested that physicians follow a checklist to conduct the procedures (Knatterud et al. 1998), and that the SOPs rationalise the medical knowledge to control the margins of mistakes derivating from medical reasoning (Bruni, Gherardi, and Parolin 2007). Data production required a deep analytical capacity of the physician, who is using his knowledge about the disease to analyse the biological evidence<sup>32</sup> (if it is necessary) and the narrative provided by the participant about his/her symptoms, which becomes a source of information for the physician for the analysis, as quotes 2 and 3 clearly illustrate. In the interaction between physician-participant, the clinical research context seems to disappear, and only reminds a physician that he is providing a service to a patient to determine his health status. At this moment, the project acquires a new character and the physician becomes the protagonist, using his previous medical knowledge as a ‘tool’ to transform the

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<sup>32</sup> Physicians required blood tests to provide a diagnostic.

information obtained from the participant and the laboratory results in a medical diagnosis. At this stage, the physician's thinking is flexible, versatile and invisible, where much of the analysis is tacit, fast and individual, at the same time addressing multiple variables and possible solutions based on the evidence collected, and he/she has the freedom to question and define what evidence is required to support his/her conclusion. As the physician narrated, at this intimate moment of reflection, he obtained a diagnostic through an internal process of propositions and associations guided by questions and answers; as a kind of flow chart that directed the mental process to provide the diagnosis. Wiig pointed out that "thinking will also rely on some of the reasoning strategies that are second nature to us" (Wiig 1993, 235). At this point the collected information triggers, priming memory, previous concepts and previous experience to provide a diagnosis. Once physicians culminated the diagnosis, the context of the project newly emerged. All the thinking processes that they conducted had to be externalised in the shape of clinical data in the medical records following the GCP and the sponsor standards.

The national regulation and the Good Clinical Practices (GCP) guide the writing of the medical evaluation in the context of clinical research. These practices emerged with the intention of standardising clinical research, increasing efficiency in the procedures, as a result of distrust in medical practices (Bijker, Sauerwein, and Bijker 2016). Then, to produce the data, physicians had to know what information to collect and how to externalise it on paper following these norms, which shaped the actions of physicians to report their results, which provided the data with a character of "correctness" to be employed to the sponsor. In the first place, physicians had to create a medical record for each volunteer, where its content was determined by the national regulation and not by the sponsor,<sup>33</sup> as the health secretary in Antioquia stated:

"You like an IPS<sup>34</sup> needs to fulfil the norm, independently of what the sponsor request, you need to meet the requirements of the medical record. We started to visit them, and they said, 'I don't have that because the sponsor receives it in this

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<sup>33</sup> In Colombia, the resolution 3374 of 2000 determines the management and minimal content of a medical record.

<sup>34</sup> Institutional Health Service Providers: All institutions in Colombia that provide medical, hospital, clinical and intensive care services.

way', 'Sorry, the norm that you need to meet to get the certification is this one.'"  
[Rep-Health secretary Antioquia, Colombia Feb-10-2015]

Then, as this quote clearly indicates, physicians working on a clinical trial must collect the information indicated in the local regulations, and not only the data requested by the sponsor. This point was corroborated by physicians, who indicated that they had to register the data as the country's normative demanded:

"The template of the clinical record was the classic one because they are patient and we have to be within the official normativity. So, we made some adjustments in the project, for the protocol, but the principal support, the core of the medical record is what is established in the Mexican official norm." [Sub-Res, Site2, SMO-3, SAVA-Mex, May-15-2015]

In addition to the national normativity, to produce the data physicians had to add to the records the information specified by the sponsor, and they had to be more consistent and explicit, as the following quote indicates:

"We are accustomed to being governed by norms. We all, despite the level of which we are at, we have to document in the record [...] here it has to be more detailed. It has to be more punctual at the beginning and at the end to avoid omissions and apply the good clinical practices." [PI-Site 4, SMO-3, SAVA-Mex, Jul-09-2015]

Then, to externalise the results of the medical evaluation of participants, physicians had to know what information to collect based on the protocol and the local regulations, and they had to know how to collect the data according to the GCPs, which are the standards of the industry. According to the GCPs, "the investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports" (ICH Harmonised Tripartite Guideline 1996, 18). As the last quote shows, physicians had to externalise as much information as possible about how they analysed the information, what evidence they employed and what conclusion they reached. Therefore, although the analytical process for making the diagnosis was flexible and researchers had the freedom to collect evidence, the writing process was governed by rules and standards decreasing the flexibility of physicians to report the results, demanding from them an effort to be rigorous and concise in the way in which they externalised data.

The process to codify their diagnosis correctly was not straightforward, as was discussed in the last chapter, which presented how physicians with extensive

experience in clinical practice found it challenging to introduce the procedures to collect information indicated in the GCPs. Nonetheless, as was reported by monitors and physicians, as the project advanced, physicians learned how to collect the data according to the GCP:

“As you repeat, you are more precise; you make a better note, you write the data better informing an adverse event. In the beginning, I made a partial note, not now. Now I know which is the item that I have to consider, when the symptoms started, when they ended, what medicines he took, how often, concomitant medication, all those aspects that I didn’t consider.” [PI-Site-1, SMO-1, SAVA-Col, Dic-10-2014]

“I had to write everything in my notes following the GCPs and each one of the mistakes to avoid suspicions that maybe I was manipulating the information.” [Sub-Res, Site2, SMO-3, SAVA-Mex, May-15-2015]

Therefore, physicians, through practice, could externalise their medical knowledge in the shape of the clinical data according to standards of the industry, including all the aspects of the evaluation, the analysis and the evidence that they employed over the visit to make their conclusions. In this way, physicians writing long and detailed notes generated credible data and decreased any suspicion that they or any other site’s members were manipulating the information. As Zollo & Winter (2002) point out, the codification of knowledge, writing down, requires a cognitive effort, especially when individuals codify their understandings. Writing becomes a mechanism to make causal links explicit and clarify ideas. In the case of writing the clinical evaluations in the medical records, physicians, in addition to writing their analysis, they had to be conscious about how they did it. Therefore, although the analytical process for making the diagnosis was flexible and researchers had the freedom to collect evidence, the writing process was governed by rules and standards decreasing the flexibility of physicians to report the results, demanding from them an effort to be rigorous and concise in the way in which they wrote the medical records.

Once this knowledge had been mastered, the know-how of writing according to the GCP standards became part of physicians’ routines. As the SMO-2 director and some practitioners working for SAVA and KINGS mentioned, they considered that physicians working in clinical trials improved their performance in their professional practice, becoming more accurate in their notes, and they also translated the knowledge acquired in the trial about data production and data management into their daily life.

This fact has also been highlighted by other researchers, who have discussed the influence of the experience gained in the clinical trials into the standard clinical practices of physicians with benefits for their patients because the level of detail paid to information gathered (Robertson and Gan 2001; Goodarzynejad and Babamahmoodi 2015). Then, the acquisition and use of know-how associated with clinical research not only has a positive impact on the data collected over the course of the research, but it also has a positive influence on the daily work of researchers beyond the boundaries of the research sites and the context of the clinical research.

#### 6.2.2.2. Contribute and improve established procedures

In addition to implementing the task indicated in the project to produce the clinical data, research sites contribute with their knowledge to improve the procedures established by the sponsor or proposing their own alternatives in those cases where room exists for it (Figure 8). One action through which sites contribute strongly to the project is in the recruitment and keeping the adherence of participants to reach the number of participants calculated by the sponsors to be enrolled in the project. Low recruitment rate has different repercussions for a trial; the length of the trial could be extended, increasing the costs; the probability of committing a type II error increases; the trial's statistical power, internal validity, and external validity of the trial decline; and finally, if participants' adherence is not good, the trial may be concluded without published results (Thoma et al. 2010; Bower et al. 2014). In contrast to the creation of the SOP, where an explicit document is created, the results of the recruitment strategy are reflected in the signing of the informed consent by the volunteers. In this case, the action of a third party (the volunteers) evidences the success of the productive enquiry (participant recruitment). This represents an extra challenge because the mobilisation of the community towards the project required a deep knowledge about the community, the project and the disease.

In theory, the personnel on the research site have the autonomy to propose the recruitment strategy with the conditions that the researcher "should be able to demonstrate (e.g based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period" (ICH Harmonised Tripartite Guideline 1996, 13) and the rights, integrity, and confidentiality of trial

subjects should be protected (ICH Harmonised Tripartite Guideline 1996, 4). Therefore, in this aspect, the research sites can contribute, proposing the recruitment strategy that they consider more convenient.

In the cases of NUSTAN and KINGE, the research sites proposed their recruitment strategy, as Dr Pablo Esmeralda [NUSTAN Chair] said: “We do not impose to the researcher how to do it [...] the researcher can do it differently since it satisfies the protocol criteria.” In both cases the site elaborated a programme and created alliances with strategic organisations such as hospitals (KINGE), social leaders (KINGE), and public TV channels (NUSTAN) and newspapers to recruit the population indicated in the protocol. In both research sites, previous experience in engaging with these allies existed, and within the research group it was considered that these strategies allowed the targeting of the specific population that they were searching for the trial. In both cases it manifested, that these strategies were successful; “the project was like a clock” – volunteers contacted the site to participate and they were committed to the project [PM R-IDVI, KINGE, Nov-05-2014]. In this way, the freedom and the experience to create a recruiting strategy to address protocol requirements allowed the site to contribute with their knowledge to create a recruiting strategy to the most critical activities of the clinical trial, the recruitment of participants and their adherence.

In contrast, in the SAVA case, the sponsor designed a recruitment strategy followed by almost all sites, excepting two in Mexico, who proposed alternative strategies based on their knowledge about local health programmes that could speed up the recruitment (details provided below). The sponsor’s strategy consisted of visiting the local schools; there, the medical team asked parents if they would like their children to participate in the research, and they collected the data of those interested to be contacted later. Those sites implementing the sponsor’s strategies did not contribute to the design of the recruitment. Nonetheless, their knowledge about the communities and about the project was fundamental to the implementation. As the sponsor in Colombia said: “They (SMOs) searched for investigators from the population, close to the people, that the people could feel identified with them; they (physicians) needed to know the problems in the region.” [SAVA-Sponsor Col, Mar-24-2015] And this close relationship allowed them to maintain the adherence of the participants to the project.



The two sites that decided to propose an alternative recruitment strategy were in the state of Yucatan. I consider their experience valuable because they used their in-depth knowledge about the community to create one of the most successful recruitment and adherent strategies of the SAVA case. In these two sites, Dr Maria Cristina Macias (PI-Site 4, Mexico) and Dr Gabriel Valderrama (PI-Site-2, Mexico) knew about the state programme to promote and closely follow up the health status of the population. This programme consisted of the assignment of one *physician, nurse and one health promoter* to communities. These two researchers proposed a recruitment strategy, creating an alliance with the local health promoters to include their knowledge about the community in the project, as both indicated in the next quotes:

**Quote 1:** “Health promoters have special relevance for me because the one [health promoter] that has less time working in his area has been there for 12 years. They know perfectly the people in each sector... They have a census, and they know which people have factors that would help us to select the subjects.” [PI-Site 4, SMO-3, SAVA-Mex, Jul-09-2015]

**Quote 2:** “One of the biggest advantages of doing this is that health promoters of the health centre actually know the entire population. They were an essential part to implement the recruitment, not only for the seroprevalence trial, but also for the clinical trial. People already know them, and they are identified with them because, for years, the health secretary has worked with them... So, it was easier because existed trust, communication, etc.” [PI-Site3, SMO-3, SAVA-Mex, Jul-08-2015]

**Quote 3:** “First, we received training from the doctor [PI Site 4] and the team, then in the information about the community structure that we have organised about the population, I review the age group that was necessary for the project.” [PHI-Site-4, SMO-4, SAVA-Mex, Jul-09-2015]

The inclusion of personnel with knowledge about the community was an advantage to recruit the volunteers. As the first quote points out, the fact that the health promoter had demographic information<sup>35</sup> about the population enabled the principal researchers to stratify their message and direct it to the potential candidates that fulfilled all the criteria to be part of the trial (i.e. age, complete vaccination schedule, two parents). Social workers were trained on the project and considered that the project benefited the communities. They employed their knowledge about the communities to direct the message to the heads of the family, as they knew their decision-making process, as one

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<sup>35</sup> In these records there is information about the medical background of each person, the enrolment of the subject into health programmes, the vaccine schedule, health reproduction, pregnancy, diarrheal programmes among others.

health visitor indicated: “I visited the house personally when the husband was there, because here many decisions are taken by the spouse, and the people invited never was insecure.” [PH2-Site-4, SMO-4, SAVA-Mex, Jul-09-2015] Then, the fact that health promoter used their knowledge about the community and integrated this with the knowledge received about the project, and that they believed in the benefits of the project for the communities, enabled the participants’ recruitment.

Another way in which these researchers working for SAVA in Mexico contributed to the project using their knowledge about the community was reducing the recruitment age of participants. In this way, they ensured the adherence of participants over the five years of the project. In this specific case, Dr Macias (PI-Site-4, Mex) knew that young males tend to migrate to the USA after high school and in the community there existed a high level of teenage pregnancy. Therefore, Dr Macias modified the inclusion criteria, as she stated: “although the project said [kids] between 9 and 16 years old, we decreased the age from 9 to 11 or 12 years to ensure the follow up” [PI-Site 4, SMO-3, SAVA-Mex, Jul-09-2015]. In this way, she anticipated the potential loss of participants as the kids grew over the course of the trial. This case shows how previous knowledge allows thinking far beyond the present conditions, proposing action to anticipate outcomes without passing through a trial and error process, as Wiig suggests (1993).

As a result of this modification, her site had the lowest levels of desertion among all research sites working for the project in Latin America, as was reported by the SMO coordinator, and this was recognised by the sponsor, who invited her to share her experience with the other sites. In this site they did not have as many desertions of pregnant women like in Colombia or the other sites in Mexico, where the index of pregnant teenagers was high<sup>36</sup> and which affected the participants’ adherence, as was reported by these sites at the interviews:

**Quote 1:** “We recruited 4500 participants, we have lost less than 5%, half of it because of teenage pregnancy.” [PI-SMO-2, SAVA-Col, Apr-01-2015]

**Quote 2:** “Recruitment was between 9 and 16 years old, some women turned 17-18 or even with 16 years old they were pregnant, we have had a good number of

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<sup>36</sup> In Mexico, according to the National Institute of Geography and Statistics, 7.8% of teenagers between 12 and 19 years have had at least one child (Instituto Nacional de Estadística y Geografía 2017). In Colombia, for 2017, 20.5% of those aged between 10 and 19 years have had at least one child (DANE 2017).

pregnant teenagers [...] for the third dosage they were pregnant, so they had only two dosages or one dosage because we could not apply it. We continue the analysis and follow up depending on the vaccines that they received and the evolution and to the baby too.” [PI-SMO-3, SAVA-Mex, Jun-24-2015]

The evidence in this sub-section is aligned with the lessons learned by Geldenhuys et al. (2012) in clinical trials after they had low recruitment rates, where they suggest that “enrolment rates should be based on accurate baseline data available on the targeted study population” (Geldenhuys et al. 2012). The data presented in this section complements their conclusion, evidencing how the use of demographic information about the community and a good understanding of their culture and decision-making process benefit the recruitment of participants into the study, complying in time and number of participants. Using knowledge about the community influenced and directed the recruitment strategy; this knowledge provided a vision of the possible outcomes of the project and its use allowed the anticipation of events. However, it is not only having the information about the community that makes a difference in the recruitment. A deep, trustworthy relationship between the parts, and good knowledge about the way in which families make decisions, and the social dynamics of the target population are fundamental to recruit the participants and ensure the adherence of the subjects in the long run. Then, the use of deep knowledge about the communities is essential to implement the socialisation and recruitment of the volunteers in a clinical trial.

#### 6.2.2.3. Address challenges

The other mechanism that evidences the integration of knowledge into the work of the research site is using it as problems emerge. One challenge usually narrated by sites was the emergence of negative rumours in the communities; the other challenge that took place in the SAVA case was the recruitment of minors for the project. In this last case, sites had to search and acquire additional recruits to the project to overcome the impasse.

Regarding the first challenge, physicians and site staff, over the project’s socialisation, had to present the project to the community. In these activities they had to already possess a good understanding of the project to solve the questions that emerged from the community and clarify any doubts that may arise. However, over this process, there

emerged “epidemiological gossip” about the project, as was constantly reported in Colombia in the SAVA case and also, I evidenced, in the case of KINGE. One example of these rumours is the next quote:

“We detected a woman that was defaming, saying that we will experiment with the kids, we went and visited her, and we said, ‘you don’t need to enrol your child in the project’, but we explained everything.” [PI-Site-1, SMO-1, SAVA-Col, Dic-10-2014]

This rumour, in the case of this site, decreased the recruitment rate and, as one researcher manifested, “gossip destroys a lot”. Therefore, to address this situation, physicians, using their contact within the community, identified the source of the stories and explained the project to them to overcome the myth and stop its diffusion. Then, through the active use of their knowledge about the project, physicians addressed this challenge and the project achieved the recruitment targets. So, this shows how once people introduce knowledge, its use is flexible, and they employ it according to the need of the project and the task to be undertaken.

The recruitment of minors in a clinical trial demands that the legal representative of the minor signs the informed consent accepting its inclusion in the project. The personnel at the site had to know the procedures and the local regulations to enrol the participants in the project. In the cases of KINGE and NUSTAN, the sites and the sponsor followed the national normativity, and they did not manifest any inconvenience over the signing of the informed consent. However, in the case of SAVA, the sponsor harmonised the informed consent process across all countries. SAVA’s sites were enrolling minors between 6 and 16 years old into the project. The regulations in Colombia and Mexico indicate that the minor’s parent or legal representative – in the singular – should provide consent allowing the minor to be a volunteer (Ministerio de la Protección Social 2008, 2008:28; COFEPRIS 2012, 4). Nonetheless, in the protocol, it was established that “after the subjects’ parents/legally acceptable representatives have signed a current IRB-approved ICF/AF, inclusion and exclusion criteria will be checked” (L. Villar et al. 2014b) - in plural. So, the recruitment established by the sponsor was stricter than the national regulations in Colombia and Mexico because either parents or legal representatives had to sign the informed consent form (ICF). This discordance between the local regulations and the protocol obstructed the enrolment of the participants in the selected communities, as the next quotes indicate:

**Quote 1:** “Both [parents] have to allow the subject to participate in the study. That complicates the situation [recruitment] because sometimes both can’t, or in these communities, 50% of women are abandoned or are single mothers where they [children] never had a father, so this is more complicated.” [SAVA Sponsor Mex, May-07-2015]

**Quote 2:** “We know that we need to apply it [informed consent] but at the time of executing the procedures and meet it is difficult, it is very complicated, especially in this community.” [PI-Site-1, SMO-1, SAVA-Col, Dic-10-2014]

**Quote 3:** “The protocol says that it must be both mother and father, you can’t, what do you want? The study? Or do you adjust yourself to someone that is sitting at a desk who wrote it?” [PI 1-Site2, SMO-3, SAVA-Mex].

In the first place, as the quotes indicate, the lack of knowledge by the sponsor of the social dimension of the communities made the recruitment process more rigid and complicated for the site personnel and created frustration, as the third quote reflects. In these communities, more than 20 % of the women exercise their motherhood without a partner<sup>37</sup> and Colombia registers the highest number, where 84% of the children have only their mother (Social Trends Institute 2015). Numbers that support the challenge that represented the recruitment of this population of the sites in Mexico and Colombia under this context, because in many cases, both parents were not there to sign the informed consent. The research site could not enrol participants without the consent of both parents, otherwise the site could be at risk of being closed because they violated the protocol. The research sites, knowing this context and barriers, had to acquire knowledge about how the legal system works and transfer it to the subject to overcome this juncture and ensure the correct enrolment of the participant in the project, ensuring the validity of the process without committing any deviation over the recruitment. To meet these requirements, personnel at the sites provided alternatives to the participants to demonstrate their legal status, like obtaining an extra-judicial statement<sup>38</sup> indicating the legal relationship between the parents and the kids, or providing legal documents that stated that kids did not have one parent. Then, personnel, using their acquired knowledge about the legal system, guide the

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<sup>37</sup> In Mexico 27.8% women exercise their motherhood without a partner. Of them, 21.3% at one point had a partner, while 6.5% are single mothers (Instituto Nacional de Estadística y Geografía 2017).

<sup>38</sup> It is a free and spontaneous manifestation, where a person in a notary under oath attested or provided information about an issue. Where the mother had to testify that the minor hadn’t had a relationship with his/her progenitor for a certain time.

participants through the legal procedures to allow the participation of more children in the trial.<sup>39</sup> Also, the staff at the site had to be proactive in searching for alternatives and learning about the legal system to face the situation, showing once again the relevance of their work in the context of a clinical trial. Based on the evidence presented in the last part, I suggest that sponsors conducting multi-national projects should follow what the local regulations indicate, rather than harmonise procedures increasing the requirement indicated in the local regulations.

In conclusion, the evidence presented in this section 6.2.2 contradicts the argument raised by Fisher (2008) about the use of knowledge of physicians in clinical trials and in their learning over the course of the trial. The results of her study in the USA indicate that “pharmaceutical clinical trials are offered to physicians as pre-packaged studies in which they choose to participate or not” where they contribute with their practical clinical skills, but not with knowledge, and they receive little training to implement the project before or over the course of the project. The data presented to this point differs from these conclusions and presents a different view about the flow and use of knowledge in vaccine clinical trials by physicians and clinical sites in Latin America.

The critical point to understand the differences in the results is in how both studies define knowledge. For Fisher (2008), physicians’ contributions are only considered if they participate in the design of the trial with ‘scientific knowledge’, which rarely occurs in an industrialised context like in the USA. Excepting if the trials are conducted by a National Health Institute, where physicians are more involved in the trial (Kagan et al. 2009, 6). In Fisher’s discussion, knowledge about the communities and participants and the use of their medical training is not considered as the knowledge that physicians use actively in the clinical trial or benefit the project. Whereas in this thesis, the contribution of physicians to the project is not only associated with the design of the project or the scientific knowledge that they can provide. In this thesis, I consider that people use different types of knowledge over the trial’s implementation, knowledge that involves the know-how that people use to implement the activities, the conceptual knowledge that people previously have and acquire as part of training, and also the

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<sup>39</sup> Personnel at the site could not be with the parents over the legal declaration because that could be considered as a coercive action. Then, the personnel at the site had to trust the will of the volunteers to carry out all the legal procedures and get the documentation, to then be part of the project.

knowledge about community, which is vital for the recruitment and adherence of participants. Researchers contribute with other knowledge for the correct implementation of the trial and data collection; they are not pre-programmed machines to produce data using a code provided by the sponsor. Therefore, reducing the knowledge contribution of physicians to only the ‘scientific knowledge’ is very simplistic and diminishes the daily contributions of the principal researchers and sub-researchers to the project to make it a success, as has been presented in this section.

### 6.3. Learning loops through the trial

The last section discussed how physicians employed their medical knowledge about the infection’s symptomatology to conduct their diagnosis. This knowledge was not static, and researchers continued learning and used the new knowledge in their medical activity, as one sub-researcher in Mexico said: “we need to be always updated, it is decisive”. In the three cases, researchers and sub-researchers indicated how, over the course of the trial, they continuously learned about masked symptoms of the disease and the management of the disease from their experience, the sponsor or the local health authorities. Physicians incorporated this new knowledge in their medical evaluation to produce the data, as this quote indicates:

**Quote 1:** “The knowledge has come from all sources. In the beginning, we only had to search for patients with fever. As the sponsor’s knowledge and our knowledge evolved, we started to search not only for patients with fever, but also if [they] had petechiae,<sup>40</sup> if they had problems of bleeding in any mucous membrane, or hidden bleeding manifested in the laboratory with haemoconcentration, anaemia. General data that orient you towards a process a little masked. In that way, we were searching. However, from all sources have come the knowledge, including the one that is transferred, the one that we get or the one that we receive from the health secretary.” [Sub-Res-Site 4, SMO-3, SAVA-Mex, Jul-09-2015]

**Quote 2:** “Well, firstly we said that dengue was fever, bone pain, muscle pain and that was all we knew about dengue. No, the problem with dengue is that it can cause other types of disorders, it can cause diarrhoea, it can be a urinary infection, what is a more masked picture, abdominal pain that can be confused with acute abdomen, with a shock for example. Then, you say good it’s a very polymorphic disease and we have had to adapt this to what you are finding. So, really, we have modified the criteria regarding dengue a lot.” [Sub-Res2-Site 4, SMO-3, SAVA-Mex, Jul-09-2015]

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<sup>40</sup> It is a small red or purple spot (1–2 mm) on the skin, caused by a minor bleed from broken capillary blood vessels (Gikonyo et al. 2008).

Therefore, these two quotes illustrate how medical knowledge about the disease was not the same and it got more robust and detailed. Showing a learning loop, where they acquired knowledge from external sources such as the sponsor and the health secretaries and introduced it into their medical activity to diagnose the disease.

One of the principal loops that takes place over the trial is the feedback provided by monitors. Loops that have been widely reported in the literature (Knatterud et al. 1998; Minisman et al. 2012; Ukwu et al. 2011a). What happens over these loops is that monitors evaluate the quality of the data produced by physicians and, usually, if too much variation is identified, additional training is provided to solve these issues and minimise the probability of future occurrences of deviations, as the next quotes illustrates:

**Quote 1:** “Yes, they need the training if they have deviations, or they are not accomplishing the times. We need to remain them the regulation, all that.” [Monitor-CRO, SAVA-Col Dic-10-2014]

**Quote 2:** “If there is a mistake we need to train the site to avoid its occurrence again.” [Monitor-CRO, SAVA-Mex, Jul-08-2015]

**Quote 3:** “Where there is an amendment in the protocol we need to retrain, when we detect on a visit or through monitoring a failure on the process, we need to retrain.” [SAVA-Sponsor Col, Mar-24-2015]

**Quote 4:** “We had meetings with the monitors, and they gave us training about modifications in the project, and if they detected that there were things that were not according to the protocol then they trained us about that.” [Sub-Res-Site2, SMO-3, SAVA-Mex, May-15-2015]

**Quote 3:** “What is expected is that those amendments and changes improve the project dynamic, improve the results and, improve the quality of the research.” [Monitor-CRO, KINGE-Col Nov-27-2014]

These loops meant that the physicians and the staff had to include the feedback provided into their work. As was presented in the last chapter, researchers working in SAVA were less permeable to the monitor comments. Therefore, the introduction of the feedback provided by the monitors was not accepted positively in all cases, and sites questioned it. However, these loops were constant and sites received regular updates of their work to improve their performance. Then, over the course of the project, a loop exists between the CRO and the site, which has the objective of improving the project quality and improving the work and diagnosis capabilities of personnel at the research site. Therefore, the lack of knowledge to implement actions is not the only trigger of



loops (Cook and Brown 1999), evaluations of external actions and reception of external knowledge trigger learning loops and constant communication to transfer the new knowledge among parts.

## 6.4. Data transfer

In the model presented in Chapter 2 the step that connects the organisations working on the interdependent project at the inter-organisational level is the transfer of knowledge and products (Ngai, Jin, and Liang 2008; M. H. Meyer and Zack 1996). In this section, I address this stage and present how sites transferred the clinical data produced to the sponsor. For firms working at a distance in knowledge work projects, the mobilisation of fragmented knowledge across firms (Bruni, Gherardi, and Parolin 2007) and the integration of data are fundamental to ensure the project's success (Anderson Jr. and Parker 2013). Also, one important element at the intra-organisational level is the storage of results or lessons learned within the firm (McElroy 1999) so the research site can increase its internal capabilities to be implemented in further research.

### 6.4.1. Transfer of clinical data to the sponsor

Anderson and Parker (2013) developed a framework to research the integration of knowledge in distributed knowledge work (DKW), like the clinical trials, where parts of the project results are produced by multiple organisations such as the clinical sites and have to be integrated by the lead firm such as the sponsor. This framework suggests that the two aspects that firm leaders must consider when designing the project are information infrastructure to promote integration and the organisational network design. These two aspects are addressed in this section to understand how the sites transfer the data to the sponsor and this sponsor, in turn, integrates the knowledge produced in multiple locations.

Although physicians collect the clinical results in the medical records, data is transferred to the sponsor in a document denominated CRF - Case Report Form. In the GCP it is established that all data collected for the study is transferred to the sponsor employing the CRF. The CRF is “a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each

trial subject” (ICH Harmonised Tripartite Guideline 1996). Nonetheless, the sponsor, as head of the project, has the freedom to define the channels to collect the data, the data to obtain, the frequency of the transfer and the procedures to receive the data produced in multiple locations. In other words, sponsors have the autonomy to define the information structure and organisational network design to collect and integrate the data; however, the boundary object to transfer the data is the Case Report Form.

In the three cases studied, the organisational network and information structure differed, which shows that in the industry this procedure is not entirely standardised. The information structure in KINGE was different to the SAVA and NUSTAN cases. KINGE was the only one that employed a combination of paper CRF and an electronic data capture software; in the other two cases the CRF was virtual. This difference had deep implications on the process to transfer data, integrate it and verify its integrity. In the KINGE case, the physician, after each consultation, based on his notes in the medical record, filed the CRF on paper manually following the ICH-GCP, a document that had three copies made with carbon paper. One of the copies was collected by the CRO monitor, as the project manager said: “CRO come [to the site] and collected it [CFR] and take it. She passed it to the data management group [sponsor]” [PM R-IDVI, KINGE, Nov-05-2014]. The CRO’s monitor was responsible for comparing if the information in the CRF complied with the ICH and it was similar to the information in the medical records. For posterity, the CRO transferred the data to the sponsor transcribing the information into the sponsor’s Electronic Data Capture software (EDC). Subsequently, the data management team verified this data. The problem with the information structure and network design were that any requirement and clarification requested by the data management team (sponsor) had to be communicated to the research sites through the monitor who, in turn, had to transfer the corrections and clarifications to the sites. This procedure created a working distance between the data management team and the research site to provide any explanation and feedback about the data. The collection of data on paper CRFs is disappearing in the industry and data is submitted directly to the sponsor data management team directly using software, which decreases the intermediation of the CRO transferring data to the sponsor, and all clarifications are requested directly through the software, as the SAVA and NUSTAN cases indicate.

In the NUSTAN and SAVA cases, the sponsor employed an eCRF (electronic Case Report Form) directly managed by the research sites, which enables a direct transfer and integration of the data. In both cases, once physicians filed the medical record electronically or physically, the data manager was the one that transcribed the data demanded by the sponsor in the eCRF. The presence of the data manager indicates how the work distribution varied in these two cases compared with the KINGE case, where the physicians and the CROs did not have responsibility for the transfer of data to the sponsor. The next quote indicates how the transfer to the sponsor was presented in the NUSTAN and SAVA cases:

**Quote 1:** “It is manual; I do the manual part [creation medical record]. Then, we have Natalia and Leandro, they put in the software; it is easy, it is not hard.” [Sub-Res-USP, NUSTA, Apr-14-2015]

**Quote 2:** “The procedure was relatively simple, there was a person that was dedicated to that, that collected the information from the medical record and transferred it to the format that the sponsor had designed. Only they had access to that, only they. I did not have access to that database because it was not my job.” [Sub-Res-Site2, SMO-3, SAVA-Mex, May-15-2015]

**Quote 3:** “When I receive the case file, I submit what the system requests, for example, the date of the visit, if the volunteer arrived, if the specific sample was taken [...], everything has to match. The process is not tedious, it is information about specific visits, but you need to be looking for the information because otherwise, you have many queries [errors] accumulated in the systems.” [PM-Site-4, SMO-3, SAVA-Mex, Jul-09-2015]

**Quote 4:** In the beginning, all the data that they [physicians] collected, we introduced it at INFORM [software employed by the sponsor]. Right now, the only thing that comes up regarding the subjects are cases of pregnancy and SAEs or terminations in a given case, but I think we only have one or two casualties. Moreover, now almost the only information updated are about the visits.” [SW-Site4, SMO-3, SAVA-Mex, Jul-09-2015]

In these two cases, physicians did not have access to the databases, so they did not control what was sent to the sponsor, although they produced the data. As quote 4 states, the information transferred to the sponsor varied according to the stage of development of the project, and the data manager was the one that had to know what data the sponsor requested. The staff transferring the data had to be quite careful in sending only the information recorded in the file without modifying the physician’s narrative, as a project manager delegated with this responsibility indicates:

“I upload to INFORM (software) what is in the file [medical record], I cannot upload anything that is not there...it is not complicated, but you have to be aware of the information to submit.” [PM-Site-4, SMO-3, SAVA-Mex, Jul-09-2015].

Then, although this activity is manual and mechanical, it demanded attention from the data managers to transfer the data. Although the transfer of data from the site to the sponsor was directly through the software, in the transfer process within the site there existed an intermediary. Consequently, the data presented about the organisational network and information infrastructure indicates that the transfer data produced by physicians is not direct to the sponsor, and there are intermediaries, either an external organisation, such as the CRO or an internal staff member, such as the data manager. In both cases there is a risk that the data produced suffer changes as a result of the transcription. In other studies, the transfer of information from the file to the CRF as the primary source of data error has been reported (Vantongelen, Rotmensz, and Van Der Schueren 1989). It has been suggested, in the literature of clinical trials, that data submitted by people that have not been delegated with this responsibility may be rejected from the database or considered with suboptimal quality because the person does not have the knowledge to do it (Knatterud et al. 1998). Therefore, the delegation of the transfer responsibility in research sites must consider the knowledge of the person to address with the software and understand the information that is transcribed to avoid misinterpretation and mistakes.

Although the process to transfer the data from the site to the sponsor varied among cases, in the three cases the sponsor employed software to integrate the data produced by the sites. This information infrastructure allowed the data to be centralised and enabled the data analysis. However, the process to evaluate the data transferred by the research site and provide feedback to the sites differed in the KINGE case compared with SAVA and NUSTAN. In the KINGE case, as was presented above, the CRO monitor was the one who communicated to the sites the amendments in the CRF and he also had to return to the original files to identify if he made a mistake in the transcription. In the cases of SAVA and NUSTAN, a person remotely connected to the database reviewed the data transferred to the site and requested clarification directly to the staff through the software. This procedure is highly shared in the industry to ensure data quality (Ottevanger et al. 2003; Gassman et al. 1995). The process to review the data by the data management team (sponsor) is presented below:

“The verification consists in identifying if there exists a mistake in the database; sometimes there are logic mistakes or other times are mistakes of consistency. Logic mistakes are, for example, that I receive a man with a pregnancy test. A consistency mistake is that a person has a headache and I name it in five different ways, which is a huge work to fix those consistencies. Sometimes the center takes time to send the data and that delays our work. For example, we request a correction, and the center is late providing the correction because the staff is busy with other activities, that is what takes most time.” [NUSTAN Chair, Apr-13-2017]

“There is monitoring of INFORM staff [actually it is SAVA data management team] who check queries [mistakes], they verify the data we submit.” [PM-Site-4, SMO-3, SAVA-Mex, Jul-09-2015]

Comparing the NUSTAN and SAVA cases with KINGE, in the two first cases the site personnel received direct feedback and questions about the data directly through the software, and they could directly solve any issue without the need for the intermediation, as in the KINGE case. Then, as it is possible to see, among cases differences also existed on the structures and mechanisms to transfer the data from the sites to the sponsor. The role of intermediaries, like in the case of KINGE, determined the accuracy by which data is transferred, but also the speed by which corrections are implemented by the sites. The use of software allows communication in real time among the parts, speeding the corrections. Then in a project where a reciprocal interdependence exists (Thompson 1967), where sub-task outcomes and inputs continuously interact, the organisational structure and communication channels established between the sponsor and the sites are fundamental to provide feedback and ensure the timely corrections of the data.

#### 6.4.2. Turnover of staff and the loss of knowledge

The lessons learned in the clinical trial by the personnel at the site becomes one of the most important capitals that the organisation has for future projects. In the literature of knowledge management, the relevance of storage the knowledge acquired by people in the organisation has been intensely discussed (Rubenstein-Montano et al. 2001; Prencipe and Tell 2001). For this, multiple authors have suggested the implementation of knowledge systems that consist of the creation of software that allows to the workers to externalise their knowledge, contacts and information into a big warehouse (Mas-Machuca and Martínez Costa 2012; Maier 2004; Pentland 1995). In the context of the research sites visited, only the R-IDVI site had implemented a kind of system to store the knowledge acquired by their workers. And I say kind of, because there was no

software to centralise all the information and it was not directly related to the clinical trial. What existed were paper formats that people filed, explaining the techniques that they had learned as part of the academic exchange. However, practical information about the clinical trial, for example, was not part of the routine. In the rest of the research site there was no software or any mechanism to at least collect the lessons learned by the workers.

This lack of mechanisms to store knowledge has an impact on the knowledge capital of the organisation for a future project, especially when there is a constant turnover of the staff over the course of the trial or between projects. For example, the Brazilian group working for NUSTAN did not have any mechanisms to ensure the transfer or codification of knowledge of the people leaving the groups, as is evident in the next fragment of the interview:

“Interviewer: How do you retain the knowledge that they (people leaving) have? Do they train new people, or do they document the process in a notebook or lab book?”

**Project Manager:** No, we don’t have that at this time [...] We have a final meeting with this person to hear his voice, to understand why and to say our impressions to this person, but we don’t have a formal document, but we have plans to have more formal documents.” [PM-USP, NUSTAN, Apr-01-2015]

Therefore, the lack of strategies to ensure the storage of lessons learned or other forms of knowledge to be transferred inside the group when a person leaves the project creates a loss of information and experiences that is impossible to recover. The project manager in R-IDVT also manifested, “The difficult thing is that the experience stays, it [experience] does not stay, the person that leaves, leaves with the experience that he had [...] the experience is not transferable. It is very hard.” Although in this research group the person leaving the project trained the new physician, enabling continuity in the process, the new physician revealed that although he received information about the project from the previous sub-researcher, he had a limited understanding of the initial stages of the project and activities conducted. So, the knowledge gained over the first part of the project was no longer part of the research group. Thus, all the lessons learned about these initial stages by people leaving cannot be employed on the site for a future project.

In two of the three cases studied, the research sites had lost staff over the course of the project. This implied that the knowledge acquired by the people leaving was no longer part of the project and the new staff had to acquire knowledge about the project, and the sponsor had to re-train personnel. In the case of sites working for NUSTAN, it was reported by the sponsor how challenging was to re-train constantly new personnel. The turnover created a problem for the continuity of the project, as Dr Esmeralda (NUSTAN Chair) indicated:

“The biggest problem has been the personnel turnover in the research sites; many people left the site, so we have to do quite often re-training... The academic work in Brazil does not allow that people have formal and competitive employment contracts in terms of salary.” [NUSTAN Chair, Apr-13-2017]

Then, although the NUSTAN case had the advantage of having a direct training channel with the sponsor to acquire knowledge and information (Chapter 5), the personnel turnover becomes into one of the grey areas of the project because people always had to be re-trained and the project on the ground did not have continuity. Because knowledge was dispersed across all the people that worked on the project at the different stages, the staff turnover meant that once the project concluded, the knowledge employed did not remain in the organisation and it was no longer available for other projects. Then, as Zhao et al. (2004) argue, outsourced companies should pay attention to how to retain, utilise and create knowledge, to improve their corporate memory and core capabilities, and develop a culture to promote knowledge sharing across the organisation. Some strategies suggested are the articulation and codification of knowledge at the project level and the creation of a mechanism for people to review the lessons learned by their partners (Newell and Edelman 2008).

The reason for this turnover in Brazil, as one of the previous quotes indicates, is the job insecurity of people in the research groups. As Laura Ferreyra (Project Manager, USP-1) explained: “we are ‘scientific bolsistas’,<sup>41</sup> we receive peer protocols, we don’t have a legal contract, it is for the project, so for technical people is more difficult to understand; they receive another opportunity, salary, and leave the project”. So, this job insecurity in the academy represents a difficulty to guarantee the continuity of

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<sup>41</sup> Expression employed in Brazil to make reference to the people that work with funding coming from scholarships provided by the university of the government which are denominated “bolsas”.

personnel that were already trained in the project and, therefore, to get the benefit of the experience gained over the execution. Although NUSTAN implemented formal and fixed contracts with the sites to guarantee certain salaries to the personnel working on the project, this did not resolve the issue. Each research group had the power to redistribute the incomes of the project and re-assign salaries. As a sponsor explained: “One of the things that we need to respect, and it is a bit delicate, is the next one. I cannot generate a distortion within the research site. One nurse of my project cannot earn one and a half times (more) than a nurse working on a routine service.” Then, because the sponsor didn’t want to create competition between the people working for the clinical trial and those that were not, they did not fix a wage for the people working on the project. Then, besides salary, some incentives and strategies should be implemented to ensure the permanence of staff in the project and the research site.

In contrast to these two cases, in SAVA’s sites, it was reported that sites’ staff were stable. Personnel had direct contracts with the SMOs, with all the social benefits, like one of the principal researchers in Colombia said: “we are directly contracted by the foundation; that generates labour stability, and that makes people perform better”. In Mexico, for example, in Site-3 in Yucatan it was reported how, at the end of the day, the team had meetings to evaluate together the results of the day, what problems they faced and how they could improve for the next days. Although they did not record on paper the lessons learned, the staff stability and the constant transfer of knowledge within the site encouraged the team to learn and improve their work dynamic. These results concord with the findings of Zollo & Winter (2002), where the socialisation of knowledge promotes the development of the group competences, although it could be more beneficial if staff or managers document these lessons.

In summary, the working conditions of the personnel are essential to avoid that all the effort made at the beginning of the trial to train staff and create a shared understanding of the project will be lost because of the turnover of staff. Therefore, both academic sites in Colombia and Brazil indicate that the labour instability in academic research sites is a threat to the project. People with the knowledge and training without optimal labour conditions are prone to leave the project to pursue a different profession, taking with them the knowledge acquired to execute the protocol.



Turnover was also frequent among CRO monitors, which is a problem in the industry in Latin America, as was highly testified by the clinical trials associations, and industry analysis indicates this too (Shuchman 2007). In Latin America, the CROs compete with each other for the best staff (Ukwu et al. 2011a). This situation creates an environment where monitors continuously look for better job opportunities, leaving the projects that are under their responsibility. This industry dynamic affected the SAVA and KINGE projects directly. In both cases, monitors changed continuously over the course of the project, which affected the projects' continuity. The person leaving the project took not only the knowledge acquired about it but also the connections and interactions that he or she had developed with the sites. So, the new monitor had to rebuild the communications channels and trust with the site's staff, as was presented in Chapter 5, and this influenced the permeability of the sites towards the information and knowledge transferred by the new monitors (Chapter 5). Then, this evidence supports the argument raised by Azoulay (2004), where he expresses a concern for the low expertise that a monitor can build about a particular project; concern that also can be extended to the turnover that takes place in the academic research organisations.

The fact that monitors and staff spend a short time in a position in a clinical trial means that they do not develop a deep understanding about the project and they do not know the previous work, so engaging with the project takes longer. It has been suggested that when people arrive as a replacement they are prone to make more mistakes in data execution, which is linked to inadequate training of the new personnel because they come late (Gassman et al. 1995). Therefore, one of the challenges in the clinical trials is to guarantee the continuity of the staff from the beginning to the end in academic research sites and CROs, which requires attention to ensure that the knowledge acquired at the beginning of the project remains in the organisation.

In conclusion, in this section, I have discussed the relevance of the know-how of the data managers in the research sites to transfer the clinical data to the sponsor. Although this activity is manual and does not require an analytical effort, it is crucial to ensure the correctness of the data transferred. Achieving this demands practice, dedication and constancy. Also, I presented how the transfer of data to the research sites consists of an interdependent activity, where the product (data) obtained in the site is transferred to the sponsor to be analysed and gather the evidence about the vaccine. In

this section, the importance of storing the lessons learned over the course of the trial was also discussed, and how the constant turnover of personnel in academic research sites decreased the accumulation of knowledge and experience in the site, so the knowledge capital that the site could have accumulated over the project is lost. Based on the evidenced collected, I discussed how, in the case of Latin America, the contractual conditions in the research sites were one of the reasons for people leaving the project and promoted the turnover (evidence about Brazil and Colombia). But also, in the case of the CROs, this turnover was discussed; however, in this case, the highly competitive environment of the CROs to attract the best talent creates the migration of people across firms, which also affected the projects, as was discussed in this section and in Chapter 5.

## 6.5. Conclusion

In Chapters 1 and 2, I presented how the clinical trial literature and the literature of knowledge management have broadly discussed the contributions of the research sites to projects. For this reason, this chapter aims to address this gap answering the research question: ***How is knowledge employed in the clinical research sites to solve the productive enquiries related to the production of clinical data and its transfer to the sponsor?***

The model proposed in Chapter 2 guided the answer to the research question. This answer has an intra-organisational perspective to analyse the use of knowledge in the research sites, and this answer also has an inter-organisational perspective to address the transfer of results to the sponsor and the loops that emerged over the project execution. The main productive enquiries in the clinical trial discussed in this chapter were: (1) the standardisation of procedures to execute the project; (2) the recruitment and enrolment of participants; (3) the medical evaluation of participants (data production) and (4) the data transfer. In this answer, I provide evidence of the positive contributions of the research sites to the execution of the clinical trial project and how they employed their previous knowledge to solve the productive enquiries. In this way, I presented how the ‘epistemology of possession’ and the ‘epistemology of practice’ (Cook and Brown 1999) converge in the execution of the project tasks.

In the first section, I presented how knowledge was integrated and employed in the research site to standardise procedures, recruit participants and produce the clinical data. In this section, I discussed two mechanisms to integrate the knowledge and information received with the knowledge of the organisation (Figure 8) to produce the knowledge products (M. H. Meyer and Zack 1996) and to give a solution to problems (McElroy 1999). The first mechanism was the standardisation of procedures through the SOPs manual. The second mechanism was the actual use of the acquired knowledge in practice of each one of the standardised activities either to produce the clinical data, to optimise the strategies proposed by the sponsor, or to overcome the challenges associated with the implementation and recruitment of participants. The integration of knowledge and its use was gradual, and it depended on the activity under execution. For example, the recruitment of participants demanded a deep understanding of the project and procedures to socialise this with the volunteers and their families, to simplify the message, and transfer it in a different language to the community. Although the protocol defined the activities to implement, and the ICH-GCP established a group of practices to develop the activities, the evidence presented indicates that the standardisation of operations was different between cases. The person standardising procedures interpreted the protocol under the light of the community dynamics and the site dynamics to propose alternatives to optimise the protocol implementation, and to address challenges that emerge over the course of the project execution.

The conceptual bases and information employed to create the SOPs and produce the clinical data were similar among cases. In all cases, the person creating the SOP had to use its knowledge about the project, the task to perform and had to know how to write the manuals according to the GCP guidelines, detailing step-by-step the procedures for each task. In this way, the person externalised her knowledge in the shape of a manual. However, the standardisation of procedures in the three cases differed considerably according to the degree of freedom that the sites had to create their manuals and the experience of the research site. Nonetheless, it is a fact that the creation of the SOPs was dominated by one person at each site or SMO where her/his vision about how procedures should be implemented prevailed, unifying practical criteria and conceptual knowledge around the trial.

The other critical task is the production of clinical data, which was an individual activity implemented by physicians. The evidence presented contradicts some of the arguments in the literature, which argue that physicians are limited to following a checklist to conduct the procedures (Knatterud et al. 1998; Fisher 2008) or that the protocols and SOPs rationalise the medical knowledge to control the margins of mistakes (Bruni, Gherardi, and Parolin 2007). Although physicians had to follow the procedures in the protocol, they had the freedom to conduct the clinical evaluation; for this, they used their medical training and knowledge about the disease, and analysed the biological evidence and the narrative provided by a participant about their symptoms to produce the clinical data. What the data presented indicates is the cognitive effort that represented for physicians to externalise the results of their medical evaluation and reasoning in the shape of clinical data that fulfilled the requirements of the ICH-GCP and local regulation. As the project advanced, physicians learned and mastered the know-how to report the clinical data according to the industry standards. Even though the evidence indicates that as researchers become more consistent and detailed in the way in which they recorded the medical files which benefited their medical practices beyond the trial context. Also, the evidence indicates that the principal researcher employing his knowledge about the community contributed to the project by proposing the recruitment strategies and tailoring the protocol to the community's social dynamics, such as the case in Mexico. The use of this knowledge is highly relevant to achieve the adherence rates in the long term. Then, not only conceptual and technical knowledge is essential to implement the project task, deep knowledge about the communities is highly positive in clinical trials. Therefore, reducing the knowledge contribution of physicians to only the 'scientific knowledge' is very simplistic and diminishes the daily contributions of the principal researchers and sub-researchers to the project to make it a success, as this section indicated.

The second section in this chapter addressed the learning loop in the project execution; these loops are at the inter-organisational level between the CRO, the sponsor or health authorities, increasing the conceptual knowledge of physicians and providing feedback on the know-how of the activity. As I presented, if sponsors identified variation in the clinical data, they or the monitors provided feedback. This situation demanded additional training or modification of procedures to solve these issues and minimise

the probability of future occurrences of deviations (Knatterud et al. 1998; Minisman et al. 2012; Ukwu et al. 2011a). Research proposing other KM models has argued that loops are a trigger because people in the organisation lack the knowledge to implement actions (McElroy 1999). However, the evidence presented indicates that in multi-organisational projects the external evaluation of results creates a learning loop induced by external actors involving a constant transfer of knowledge among parts. Therefore, the internal demand for knowledge or external knowledge induced loops.

The last section of this chapter explained, at the inter-organisational level, the transfer of data to the sponsor and the strategies designed by each sponsor to centralise the data, and at the intra-organisational level, I discussed the relevance of storing the lessons learned for future projects. Regarding the data transfer, I evaluated two aspects proposed by Anderson and Parker (2013) to integrate knowledge in distributed knowledge work (DKW): the information infrastructure and the organisational network design. This last aspect corresponds to the structural dimension to transfer knowledge to the research sites addressed in Chapter 5. In the different cases, the sponsor defined the channels to collect the data, the data required, the frequency of the transfer and the procedures to receive the data produced in multiple locations and integrate it. These four elements differed among the three cases, showing that the integration of data is not entirely standardised in the industry. In the first place, the information structure in the KINGE case differed to the NUSTAN and SAVA cases. In the KINGE case, a combination of physical documents and electronic platforms to transfer information was employed, where the CRO monitors played an important role in the data transfer. This last element created a distance between the sponsor's data managers and the site to determine any variation in the data and provide feedback. In contrast, SAVA and NUSTAN employed a bi-nodal software, where the sites directly transferred the data to the sponsor. In these two cases, the intermediaries transcribing the data were on-site personnel and feedback provided by the sponsor was direct and in real time. As I presented, these differences had implications on the transfer and the process to verify it. Then in a project with reciprocal interdependences (Thompson 1967), where sub-task outcomes and inputs continuously interact, the organisational structure and communication channels established between the sponsor and the sites are fundamental to provide feedback and ensure data corrections on time. This

evidence indicates that in the model proposed to study the flow of knowledge in a multi-organisational project, it is necessary to consider the loops that emerge across organisation when organisations transfer interdependent products.

Finally, this chapter discussed how the turnover of personnel and the lack of knowledge system to store the lessons learned decreased, over the project, the capacity to use the experience gained in future activities. None of the sites visited had a proper strategy or procedure for recovery and transferring the knowledge developed by people working on the project before leaving, creating gaps and loss of knowledge to the organisation, impacting the organisation's knowledge capital. This section evidenced how the labour conditions of the researchers and staff members incentivise staff turnover. It was evident that in countries such as Colombia, Brazil and Mexico a competition exists between CROs for qualified personnel, which promotes the turnover, which affected the relationships between the CRO and the sites and the transfer of information, as I discussed in Chapter 5. Also in countries such as Brazil, the high demand for trained physicians in clinical research promotes turnover, especially in an academic context, where salaries are not as competitive as the industry. Therefore, the staff turnover in the organisation becomes a threat for the creation of knowledge capital in the organisations, and outsourced organisations should consider a mechanism to retain their staff and create a culture to promote knowledge sharing across the organisation, so it is possible to create a corporate memory and enhance the organisation's core capabilities.

# Chapter 7: Discussion and Conclusions

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## 7.1. Introduction

With the last empirical chapter, I concluded the study of the flow of knowledge across organisations participating in multi-organisational clinical trials in Latin America. In this journey, I have paid attention to the transfer, acquisition and use of knowledge, information and data in the clinical trials to produce their respective knowledge products. I studied the design of the project with the creation of the clinical protocol, addressing its transfer to the research sites, the acquisition of knowledge by these actors and the integration and use of knowledge to produce the clinical data and its subsequent transfer to the sponsor. In this final chapter, I will bring together the empirical, theoretical and practical findings presented in the chapters above to answer the principal research questions that started this doctoral journey: **How does knowledge flow across organisations and is employed by people in their firms to implement the clinical trials and obtain their respective results?**

As a result, studying three clinical trial projects, I explained the analytical process that led to the transformation of initial knowledge (conceptual, contextual, practical) on tangible results, “boundary objects” later transferred either within the organisation (SOPs) or across organisations (protocol and data). The knowledge acquired was consistently involved in the action of research site staff, in activities such as the enrolment and adherence of individuals over the course of the clinical trial or the contribution and reshaping of initial actions that allowed them to face emerging challenges. Also, in this mapping process, I informed the factors that influence the transfer and acquisition of knowledge at the inter-organisational level, such as the structure to transfer and integrate data, knowledge and information, the knowledge-base of people to acquire knowledge, and the permeability of people to acquire knowledge. This last factor is a concept proposed, elaborated and evaluated over the course of the empirical chapters.

In this thesis a three-step model was proposed based on models reported in the literature of 'knowledge models, work and processes' (K. Grant 2011, 121), the concept of interdependency proposed by Thompson (1967), and the three factors that influence the transfer of knowledge across organisations to study the flow of knowledge, data and information. The three steps are: (1) The acquisition of knowledge, data and information by people. (2) Integration of knowledge and its use in the practice (knowing) to solve the productive inquiry and evaluate results. (3) Storage and transfer of results to other organisations. Then, I identified the products that created interdependency across organisations and were directly linked to the production of the clinical data in the clinical trial. The clinical protocol and the clinical data were identified as the primary products. Then, I formulated three questions to understand how the sponsor and the research sites employed, acquired or transferred knowledge, data and information to produce the protocol and the clinical data. These three research questions guided this research, and the three empirical chapters of this document addressed each question separately.

The conceptual framework proposed in the theoretical framework was robust, to follow the flow of knowledge, data and information in different organisations participating in the project, from the design of the protocol until the production of the clinical data. However, the analysis of the data collected also pointed out that the model proposed initially had to consider another dynamic to better explain and study the knowledge flow in a multi-organisational project. In this chapter, in the first section, I will provide a summary of the main empirical findings associated with the production of the protocol and clinical data and the flow of knowledge in a clinical trial for vaccines in Latin America. In the second section, I present several noteworthy contributions of this research to the study of knowledge management in outsourced projects or services. Here is proposed a model that brings together the intra-organisational and inter-organisational dimension of the knowledge flow, and simultaneously shows the transformation of the knowledge in different interdependent knowledge products that leads, at the end, to the expected result.



## 7.2. Main empirical findings

The discussion about the development of new vaccines or medicines in developing countries has focused strongly on the mechanism to develop the product, its introduction into the market (Srinivas 2006), the development of capabilities either for the drug evaluation (Hanlin 2008) or their production (Chataway, Tait, and Wield 2007). Nonetheless, the understanding about the clinical evaluation of the new product and the challenges of the clinical trials on the ground, especially in endemic rural areas, has been less discussed. Although there have been papers narrating the experiences or lessons learned by physicians and companies implementing clinical trials (Campbell et al. 2007; John 2006; Zaman et al. 2012), these studies have focused only on one of these two actors. These studies have paid less attention to the relationship among the parts, and the knowledge employed by the actors in the trial. Moreover, the implementation of clinical trials in Latin American countries has been under-studied compared with other regions such as Africa (Geldenhuys et al. 2012; Vischer et al. 2016; Gikonyo et al. 2008) or Asia (Abbas 2007; Zaman et al. 2012), where sponsors share their experience implementing trials in these countries. Therefore, this study addressed these gaps and provided an understanding of how knowledge is transformed in clinical trials taking place in Latin American countries.

### 7.2.1. Empirical findings, the first research question

The first sub-research question of this thesis was: ***How did the sponsor acquire and use knowledge, data and information to design the clinical protocol?***

This question emerged because of the gap in the literature about the acquisition and use of knowledge to design the clinical protocol. Researchers have extensively discussed the need for a multidisciplinary perspective to design the protocol (Chin 2012), the interaction of people writing the protocol, the physical writing of the protocol process (Eapen 2007; Gennari et al. 2004; Weng et al. 2004; Weng et al. 2007) and the need to address aspects such as scientific and logistic issues, data management, implementation and data analysis (Ottevanger et al. 2003; Goodarzynejad and Babamahmoodi 2015; Pocock 1980). However, the need for external sources of information and knowledge and the use of knowledge residing within the clinical team boundaries were less discussed. From the literature, it was possible to infer that one of

the challenges is to integrate multiple versions over the writing process (Eapen 2007; Gennari et al. 2004; Weng et al. 2004; Weng et al. 2007), and that the protocol creation has been considered a routine activity where clinical teams have the knowledge and experience to do it. However, the evidence provided in Chapter 4 provides new evidence to the protocol creation process, showing how clinical teams required constant interaction with external sources to acquire data, knowledge and information to use in their analysis to create the protocol.

The empirical findings in this study provide a new understanding of the knowledge employed to design the protocol. This study has found that five groups of data, knowledge and information are critical to designing the protocol. (1) The knowledge and experience of the clinical team. (2) The previous results of pre-clinical and clinical phases. (3) The guidelines designed by the WHO to evaluate the vaccine and implement laboratory tests to measure antibodies in humans (two different guidelines). (4) Sponsor's commercial interest. (5) Operative and social information and epidemiological data about the disease incidence and prevalence in the locations when the trial took place (Table 3). In all cases, sponsors employed these pieces of knowledge and information in the design of the protocol. What varied among cases was the availability of this knowledge and information within the boundaries of the clinical team, which triggered the acquisition of this missed information and knowledge.

The evidence from this study suggests that in Latin America, research institutions lack the knowledge and experience to lead clinical trials for new medical products, which makes it challenging to recruit personnel with this knowledge to close knowledge gaps. The evidence suggests that once firms identify individuals with the background to design the protocol and lead the project, this personnel, in turn, translated their personal experience to the project design and closed their knowledge gaps through a learning effort (Akbar 2003), employing, as a base, the conceptual bases possessed by individuals. The NUSTAN case illustrates how, in cases where the personnel do not participate in the previous trial, ensuring a communication channel with personnel involved in earlier stages allows access to the knowledge that the team cannot recreate internally (Powell, Koput, and Smith-doerr 1996).

The use of guidelines to design clinical trials is a shared practice in the clinical trial industry. However, the use of the guidelines is usually not reported in the literature as part of the knowledge and information employed by clinical teams to design protocols and the clinical trial, it is taken for granted. These findings suggest that, in general, sponsors employed published guidelines as starting point to design their protocol for the vaccines evaluated. In the three cases, it was evident how the guidelines developed by the WHO were the backbones to design the protocols and conduct the laboratory tests. Then, all three cases shared this same information to create their protocols. As one researcher said, it was a “template” to create the protocol. Which clearly indicates its relevance for the study design. However, not all the guidelines were similarly accepted and used in all cases. The NUSTAN case evidences how critical positions about these documents reduced the use of materials widely accepted in a community and it generates a resistance to use its content under the light of the scientific premises of their clinical research. Therefore, the results of this investigation show that knowledge of the teams to interpret the guidelines reshaped the use of the guidelines, despite its standardising role to create knowledge products.

Another aspect that is usually neglected by those discussing the protocol creation is the influence of the commercial interest of each sponsor on the design of the clinical trial. Findings reported in Chapter 4 indicates that the commercial interest defined the population included, the sample size and if the clinical trial would be multi-national or in a single country. So, the commercial interest reshaped the information required to design the protocol. Also, this interest demanded efforts to consolidated coordinating teams in multiple countries (SAVA case in Brazil) and outsource the project to CROs in multiple countries which later had a repercussion on the knowledge transfer. Then, this aspect must be considered as a factor to reshape the protocol design and goes beyond scientific interests.

Continuing with the answer to the research question, to create the protocol clinical teams acquired knowledge, data and information from external sources. This acquisition was mediated by two factors the channels employed to access to the sources and the permeability of the clinical team towards requested and not requested information and knowledge. As the cases studied indicated, the geographical distance between the source and the clinical team, and the previous linkages among the parts,

determined if the clinical team accessed the information directly or the clinical team required the use of boundary spanners. In those cases where a geographical separation existed, but a direct communication channel with the source existed, sponsors requested the information directly. However, as the SAVA case illustrated, if there were no communication channels among the parts, the use of boundary spanners was necessary to support the search of information and data and help with the transfer of data. Also, the data indicate that geographical separation gives place to the emergence of boundary spanners-in-practice (Levina and Vaast 2014), who assume a boundary spanning role not delegated by the sponsor, which creates fragmentation in the knowledge and information transfer. As the evidence indicated, boundary spanners are active actors who interact with the data and process it before being sent.

In summary, in Chapter 4 I provided new evidence about the protocol creation process, showing how clinical teams constantly interacted with external sources to acquire data, knowledge and information and used it to create the protocol. Also, I provided empirical evidence about how they employed or criticised guidelines in the design of clinical trials, a topic that scholars usually do not report and is a shared practice in the industry.

### 7.2.2. Empirical findings answering the second research question

The second research question in this thesis was: **To what extent does the structure designed by the sponsor to transfer knowledge, the permeability of the research sites, and the previous experience of people working on the project influence the acquisition of knowledge in the research sites?**

Within the clinical trial community, researchers have associated data's validity with the level of training that the sponsors provide to the personnel working in the clinical trial about the protocol (Gassman et al. 1995; Subramaniam and Dugar 2012), or training on the GCP and the project documentation (Ukwu et al. 2011a). However, the discussion has been limited to highlight its relevance, but the literature has not discussed or presented empirical evidence about the training implementation and the factors that influence the knowledge acquisition. Also, in a changing context, with the presence of new actors like the CROs and SMOs, little has been researched about the influence of

these actors on the acquisition of knowledge, with few exceptions that discuss the knowledge losses for research and technology because of the presence of CROs (Lowman et al. 2012). For this reason, studying the training and transfer of knowledge becomes relevant to analyse the flow of knowledge between the sponsor to the research site and the creation of an understanding about the project and the task to undertake to produce the clinical data across research sites. This chapter addressed three factors that played a role in the transfer and acquisition of knowledge. Firstly, the structure designed by the sponsor to transfer knowledge. Secondly, the permeability of the research sites, and thirdly, the previous experience of people working on the research sites.

In the first place, the chapter presented evidence that the structure designed by the sponsor to transfer the information about the project to the research sites had a direct influence on the acquisition of knowledge by the site. In the clinical trials, three key elements defined the structure of the network: direct communication between the site and the sponsor, the outsourcing of the project to a CRO, and the outsourcing of the creation and management of research sites to SMOs. Direct communication between the site and the sponsor allowed a simple transfer of knowledge and information required to implement the project. In contrast, the data presented elucidates how the decisions of the sponsor to outsource activities related to the transfer of information and training to the CRO and SMOs had a clear implication on the flow of information between the sponsor and the site. The consequences of the presence of the CRO in the transfer of information were (1) the slowing down in the communication between the parts, (2) the emergence of gaps in the transfer of information and (3) the co-presence of the SMO and the CRO to transfer information created confusion and lack of trust on one of the sources. A bifurcated structure to transfer information rather than provide continuous support to the sites to acquire the knowledge and information created confusion on the sites because each source offered different versions regarding how to implement the trials. This chapter also contributed to the discussion about permeability initiated in this PhD and shows an association between structure and permeability. This study has found that trust in the source was the key enabling factor that modulated the permeability of the staff towards external sources, and this trust depended to a large extent on the experience of the person transferring the

information. Therefore, the empirical evidence indicates that a reduction in the number of sources employed to transfer information increases the efficiency in the acquisition of knowledge and increases the permeability of the sites to receive the new information.

The data presented about the outsourcing of the project to CROs elucidated a deeper problem in the industry in Latin America. Although outsourcing can give results on decreasing costs, the evidence presented indicates that this intermediary, rather than contributing, represents an obstacle to the management of knowledge over the course of the trial, especially in the initial stages, where staff at the research sites build their knowledge about the project and the work to undertake. The distribution of responsibilities within the CROs to train the monitors and transfer the information to the sites has a direct consequence on the efficiency to transfer knowledge and information to the sites. The fact that information sent by the sponsor passed through multiple staff inside the CRO affected the final information received by monitors responsible for the final delivery. Therefore, if any information was missing on the way, it was likely that the sites did not receive all the information.

The evidence in this chapter presents a new scenario, what does happen when the local researchers do not have the experience to implement the protocol? Usually, it is reported, in the literature of clinical trials, how sponsors work with trained physicians that have the experience to conduct the project (Cruz and Gagnon 2011; Kennedy 2001; Petryna 2006). However, in the SAVA case, this was not the case in most of the project sites, which gave the opportunity to understand the relevance of the knowledge-base on the acquisition of knowledge in a clinical trial and explore a new scenario. All the staff interviewed in all cases at least had a technical or professional knowledge from which they built and reinforced the concepts required for the project, so they had a conceptual knowledge to build new knowledge. However, the process to build the practical knowledge to implement the trial following the procedures indicated in the ICH-GCP and the sponsor was more complex in new research sites compared with experienced sites.

In the cases of NUSTAN and KINGE, the opinion leader had a research group to execute the project, and a large part of the personnel had the conceptual basis and the

experience to understand the new project and implement it. This previous knowledge allowed the identification of the gaps in the information transferred by the CROs and enabled the training of new personnel. Experienced personnel constantly shared their knowledge with new staff, and within these research groups, spaces exist to socialise and learn from another project and members; in these cases, learning practical knowledge had a strong component of example. In the case of SAVA, the new sites learned from experience (Pentland 1995) thanks to an innovative pre-trial that allowed the integration of the acquired knowledge into their routines and practices, a learning process that had a large component of learning by doing and trial and error. Unfortunately, staff in new research did not coexist with experienced researchers and the interaction with experienced personnel was limited to training visits, and the learning in practice was alone. Then, the possibility to solve doubts immediately and replicate a practice was low; only after the results were obtained was it possible to identify if staff followed the instructions and the guidelines – only at this point corrective actions took place. Therefore, the constant presence of a person with the experiential knowledge transferring this knowledge and providing examples makes a difference to the speed of the knowledge acquisition of new learners, especially in those cases where an entire team lacks the practical knowledge to implement a clinical trial.

One empirical finding in this chapter was the influence of the local regulation to implement clinical trials in Colombia on determining the professional profiles of the people working in clinical trials. This regulation demanded a redistribution of responsibilities in an experienced research site, which disrupted the team dynamics. The staff that had, in the past, implemented activities associated with blood and drug handling could not employ this accumulated knowledge in the new project because the regulation excluded their professions from the list of professions that can process samples or handle the research product. Then, this situation demanded an internal exercise of hiring new personnel and training them to do the work of personnel that already had the knowledge to do it. Then, in the case of Colombia, the local regulations had a direct influence on how the previous experience and knowledge could not be employed directly in the execution of the clinical trial.

In summary, in Chapter 5 I provided new empirical evidence about the influence of the structure created by the sponsor to transfer knowledge and information to the research

sites, showing the impact of intermediaries in this activity. Also, this chapter provided evidence about how CROs influence the transfer of information and their internal distribution of responsibilities affects the information flow directly. Another empirical aspect highlighted was the acquisition of knowledge in newly constituted research sites, which is an atypical case in the context of clinical research. This evidence presented the process of learning by doing lived in these organisations and how the strategies designed by the sponsor to develop practical knowledge in these sites had a positive effect on the acquisition. Notably, the empirical evidence indicates that, in Colombia, the entry into force of new clinical research regulation influenced the knowledge-base available to implement the trial and demanded a re-distribution of responsibilities and training of new personnel.

### 7.2.3. Empirical findings answering the third research question

At the transition stage, before initiating the clinical trial, the transfer of knowledge by the sponsor and the acquisition of this by the research site was discussed. Then, in this study about the flow of knowledge and its use to produce knowledge products over the course of the clinical trial gave place to the third question: ***How is knowledge employed in the clinical research practice to solve the productive enquiries related to the production of clinical data and its transfer to the sponsor?***

One of the main contributions that I'm doing is opening the black box of the research sites, explaining how physicians produce clinical data and how personnel at the site contribute with their knowledge to the project execution. Previous studies about knowledge management in the pharmaceutical industry have discussed: the relationship between the pharmaceutical company and the CROs (S. Gupta and Polonsky 2014); the hierarchies in the transfer of knowledge and knowledge creation between CROs and the pharmaceutical (Azoulay 2004); the risk of losing knowledge by the pharmaceutical company and their dependency on external suppliers (S. Gupta et al. 2009); the influence of the staff behaviour on the integrity and safety of the subjects and the procedures to recruit participants (Ottevanger et al. 2003; van Dongen 2001; Ippoliti 2013; Barnes and Florencio 2002b; Barnes and Florencio 2002a; Geldenhuys et al. 2012; Goodarzynejad and Babamahmoodi 2015). Also, researchers have documented



the problems emerging in the trial implementation, including protocol violations, consent violations, fabrication of data, falsification of data and financial conflict of interest (Habermann et al. 2010; Gardner, Lidz, and Hartwig 2005; George 2016). To address these problems, the literature has proposed multiple strategies to improve data quality in clinical trials in general (U.S. Department of Health and Human Services Food and Drug Administration 2006; Friedman et al. 2015; Chan et al. 2013; Gassman et al. 1995; Knatterud et al. 1998; Meinert 2012). However, the work and contributions of the research sites have been broadly discussed by practitioners in the industry and less addressed in the literature of knowledge management. One of the reasons to focus the discussion on the CRO is the way in which private funded clinical trials are implemented in the USA and Europe. In these regions, the biggest CROs have their own research sites to implement the trials, which differs from the operational model of the CROs in Latin America, where CROs do not have their own research sites and need to re-outsource the project implementation to local research sites or principal investigators. Then, it is in the context of Latin America and specifically vaccine trials that the discussions in this thesis have been taking place.

The integration of the protocol to the research site activities took place through two complementary mechanisms. In the first mechanism, personnel at the research site created SOPs manuals to operationalise the knowledge acquired from the sponsor. In the second mechanism, people directly used the acquired knowledge in practice to recruit volunteers for the project, to produce the clinical data, to overcome the challenges associated with the implementation and to optimise procedures proposed by the sponsor. However, this integration with the previous knowledge and use of knowledge transferred was not straightforward: the organisational context and the context of the communities in which the trial took place influenced this integration.

In the cases studied, one person per site created the SOPs. The vision of this person about how procedures should be implemented dominated the integration of knowledge into the site routines. People creating the SOPs in the three cases shared three elements. They had the complete understanding of the research sites, and how to execute the project task, they had experience in clinical research, and they had a good understanding of the protocol. The evidence indicates that although the SOPs governed the actions of the personnel participating in the clinical trial and settled the day-to-day

activities, these documents were not perfect and their implementation in the sites does not mean a full standardisation of procedures. Even though key opinion leaders have suggested that regulatory authorities or the sponsor should evaluate the manuals created by the sites before initiating the project. The deviations on procedures are an indicator of why creating SOPs is not enough to standardise procedures and how the full understanding and implementation of the procedures in practices is necessary to standardise the procedures. The standardisation of procedures in all cases did not mean a high control of the routines or a reduced number of opportunities for staff to contribute to the project. However, if there is a central and rigid managerial control, such as in the case of the SMO-2 in Colombia, the freedom of the site's staff to contribute to the project and the standardisation of procedures decreased.

Physicians had the freedom to use their knowledge to provide their diagnosis despite the standardisation of procedures. In the cases studied, the production of clinical data demanded an understanding of the protocol. However, the main knowledge capital to produce the clinical data was the medical experience of physicians, their analytical skills and their practical knowledge to externalise the clinical data following the industry standards. Data production required a deep analytical capacity of the physicians to evaluate the biological evidence and the narrative provided by a participant about their symptoms. As the evidence indicates, physicians had the experience to provide a medical diagnosis, but the practical knowledge to externalise the data according to the ICH-GPC was developed over the course of the trial through a feedback loop process between the monitor, the sponsor and the physician. The evidence indicates that physicians to externalise data had to follow the national regulations and, in second place, procedures indicated in the ICH-GCP. The procedures established by the sponsor cannot be above the procedures and information required in the national regulation. The fact that experienced physicians faced more difficulties to follow the GCP to collect the data compared with less experienced physicians indicates that if a practice is deeply rooted and practitioners have established working routines, the introduction of new practices or modification of the old ones takes longer than if the person hasn't developed a routine to implement an activity. Therefore, this study shows how beliefs and resistance to change are elements that influence the activities performed and caused bias in the results, as Knatterud (1998) suggests.

The evidence from this study suggests that, in the design of the recruitment strategy and its implementation, the use of the knowledge about the social dynamics of the population by the researchers contributes enormously to the project success. The evidence about the two research sites in Mexico working for SAVA showed how using the accumulated knowledge about the community (migration patrons, teenage pregnancy) and a good understanding about the project favoured the recruitment of volunteers. In the long term, this knowledge minimised the risk of lost participants over the course of the project. Also, the creation of alliances with local health programmes allowed the integration of local health workers, who had profound knowledge about the community. So, their experience and contextual knowledge became an advantage to create an alternative recruitment strategy that better addressed the project needs.

Also, the deep knowledge about the communities allowed sites to face threats that emerged because of the presence of rumours or the limitations raised, because the social realities of the communities intervened. For example, the knowledge about the social context from the leaders and the members of the community allowed the building of trust between the communities and the research sites and dismantled chains of gossip that emerged in the community about the project. The social reality in the territories has consequences for the project implementation if these are not considered in advance. The lack of contextual knowledge by the sponsor to establish the inclusion criteria gave place to a series of challenges to recruit participants. Local researchers faced this situation using their knowledge about the local legal system and guiding the parents through the process without intervening directly in it. Therefore, the present study enhances our understanding of how research sites, especially physicians, employ the knowledge about the communities in the clinical trials to create and implement the recruitment strategy.

The transfer of data from the research site to the sponsor marks the end of the productive work of the research sites and the initiation of the data analysis by the sponsor to obtain the clinical evidence. This fact creates a reciprocal interdependency between the sponsor and the research sites, where the sponsor constantly requests clarification on the data from the sites. In the three cases studied, each sponsor defined a different organisational network and information structure to integrate the data, showing that, in the industry, this procedure is not entirely standardised. The presence

of intermediaries to transcribe data from the medical records to the CRO or the electronic data capture induced mistakes and created feedback loops to clarify the information. The presence of the CROs in this transfer process showed, once again, a negative effect, as they did not have the original sources on hand, decreasing the speed of reviewing the data. In contrast, a direct communication site sponsor to transfer the data enabled a direct feedback loop and a faster evaluation of the data.

The evidence collected also suggested the negative effect of personnel turnover on the continuity of knowledge in the clinical trial. The lack of a mechanism in the research sites to manage the knowledge acquired by the staff and to ensure the transfer of knowledge to the team creates a loss of information and experiences that is impossible to recover. One of the reasons for the staff turnover was the labour stability in the research sites in Latin America. The job insecurity in the research sites represented a barrier to guarantee the continuity of personnel that were already trained in the project so the site could not get the benefits of the experience gained by the staff over the training and the execution. Therefore, ensuring the working conditions of the personnel in the clinical trial is essential to avoid the loss of staff and of all the effort made at the beginning of the trial to train staff and create a shared understanding of the project.

The results of this study have shown how knowledge, data and information flows across organisations, and it is used by the sponsor and the research sites to execute their parts in the project, in this way answering the main research question of this thesis. ***How does knowledge flow across organisations and is employed by people in their firms to implement the clinical trials and obtain their respective results?*** This research extends our knowledge in the first place about the use of knowledge within the research sites to collect the clinical data. The evidence presented indicates that teams employ knowledge acquired from external sources in the various tasks associated with the project implementation. Nonetheless, the process to incorporate the new knowledge by people in their routines was not straightforward and demanded an additional effort before it was fully integrated into the routines and combined it with the know-how that personnel already had. Also, this work dived, for the first time, into the knowledge about the social context that research sites have and how the use of this contributes directly to the project implementation and its success. Therefore, these

findings enhance our understanding of the use of knowledge within the research sites and contradicts the vision that research sites are only data makers and do not contribute with their knowledge to the project.

### 7.3. Theoretical discussions

This study proposes a model to study the flow of knowledge, data and information and its transformation in multi-organisational projects at the intra-organisational level and inter-organisational level. The model proposed in the theoretical framework was built based on three previous models of the literature of knowledge “models, work and processes” (K. Grant 2011, 121) introduced by Meyer and Zack’s cycle (1996), McElroy (1999), and Ngai (2008). These models have three stages in common: the acquisition of knowledge, the task execution, and the transfer/storage of the results which were adopted in this research as a base to create the model to study the knowledge flow (Table 4). The three steps were complemented with the concept of interdependency proposed by Thompson (1967) to explain the relationship between outcomes and inputs among firms that takes place in the context of outsourced projects or multi-organisational projects. Also in this model the critical enabling factors that mediated the acquisition and transfer of knowledge were considered. Regarding knowledge acquisition, the factors identified were the previous experience of the organisation and the permeability of individuals to external information. Regarding the knowledge transfer, it was identified that the structure established by the sender to reach the receptor could be a relevant factor in the transfer of information (Blumenberg, Wagner, and Beimborn 2009). In this section, I discuss separated each one of these steps and the emergence of new facts that I consider relevant to include in a reviewed version of the model proposed.

#### 7.3.1. Knowledge transfer and the role of intermediaries

The work on interdependency has focused on the interaction between two nodes, the flow of work, the complementarities of the different work products, communication, control and interaction between the unit executing pieces of work (K. Kumar, van Fenema, and von Glinow 2009). However, to my understanding in this field of work, the presence of intermediaries as a mechanism to reduce costs and communicate with other organisations in distributed work has not been considered. Then, this work is the

first one in the context of sequential interdependencies that addresses and develops this issue, showing the role of these actors in these activities.

**Table 4. Summary of the conceptual model proposed to study the flow and use of knowledge over the course of a multi-organisational project.**

	<b>Intra-organisational dimension</b>		<b>Inter-organisational dimension</b>
<b>Stage</b>	<b>Acquisition</b>	<b>Task execution</b>	<b>Transfer</b>
<b>Analytical concepts</b>	<ul style="list-style-type: none"> <li>• Permeability.</li> <li>• Previous experience.</li> </ul>	<ul style="list-style-type: none"> <li>• Use of knowledge to produce the product.</li> </ul>	<ul style="list-style-type: none"> <li>• Structural dimension to transfer the product and other information.</li> <li>• Interdependency.</li> </ul>

Scholars such as Samoilenko and Nahar (2011) have argued that the client is the one responsible for planning and conducting the training and transferring specific and generic<sup>42</sup> information about the tasks to be implemented for the project to the contractor. The evidence presented in this thesis supports this argument. However, it shows that the transfer is not always direct between the source and the receptor, as Samoilenko and Nahar (2011) suggest, and it is implicit in the model proposed based on Meyer and Zack's cycle (1996), McElroy (1999), and Ngai (2008) (Table 4). The data presented shows that the delegation of this responsibility to a third party has a direct consequence on the transfer of information and its acquisition by the receptor. Although, the evidence collected indicates that the sponsor directly transferred information related to the protocol, the outsourcing of training to intermediaries such as the CROs and SMOs affected the information transfer. Therefore, in outsourced projects, the actors transferring knowledge and information to the same receptor in multi-organisational projects simultaneously is evident, which, as I have highlighted multiple times, had direct consequences on the transfer process.

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<sup>42</sup> Zack defined general explicit knowledge as a broad knowledge that is independent of particular events, while specific knowledge or information refers to knowledge that is context-specific, where specific categories and descriptions should be provided (Zack 1999).

The literature names these intermediaries as boundary spanners. It has been argued that these actors emerge as a solution to manage the boundaries (Levina and Vaast 2014), linking groups separated by location, hierarchy or function (Ansett 2005; S. Gupta and Polonsky 2014; Levina and Vaast 2014; Alavi and Leidner 2001). However, the evidence presented indicates that the role of these boundary spanners does not always benefit the transfer of knowledge and information across organisations. The emergency of boundary spanners-in-practice decreased the interaction among organisations, and these spanners were active actors who interact with the data, processing it before sending it. Then, as Meyer (2010) suggests, boundary spanners or knowledge-brokers do not only move knowledge, they also produce “brokered knowledge” and transfer it across boundaries.

Delving into the discussion about the presence of intermediaries at the inter-organisational level, Blumenberg et al. (2009) suggested that the transfer of knowledge from the outsourced to the contractors has two dimensions: a contain dimension and a sender-receiver dimension (structure dimension). This last dimension explicitly defines in a document how the interaction between the parties should be. The structure dimension proposed by Blumenberg et al. (2009) has its roots in the hierarchical structures to transfer knowledge within the firm proposed by Nickerson and Zenger (2004). These authors agree that the efficiency of the transfer of knowledge is related to having a defined interaction structure to transfer the information and, in turn, this helps to create a high level of shared knowledge. Also, the literature suggests that in interdependent tasks the amount of communication and coordination effort among parts is highly relevant (K. Kumar, van Fenema, and von Glinow 2009). The findings of this project indicate that not only is it necessary to have defined structures and clear rules, as Nickerson and Zenger (2004) and Blumenberg et al. (2009) suggest. The complexity of the structure also has implications on the transfer of the results from one firm to another. Chapter 5 evidenced how simple structures with direct communication between the parts were the best mechanism to transfer information about the project between the sponsor and the research groups. In contrast, structures with one or two intermediaries between sites and the sponsor affected the transfer process despite the existence of written down protocols of communication. Moreover, if the intermediary organisations have a complex internal structure to transfer information, or there are

multiple intermediaries with overlapping responsibilities on the transfer of information, the transfer is negatively affected.

The results of this research strongly indicate that the presence of intermediaries in outsourced projects, rather than enhancing the transfer of information, data and knowledge, it slows down the transfer process. Their presence creates knowledge gaps and misunderstandings, and makes the entire transfer process inefficient compared with the case in which communication between the sponsor and the sites was direct. Also, as the SAVA case illustrates, these complex structures have profound implications for the acquisition of knowledge by the research sites, also having a direct link to the receptor's permeability towards the source and the information and knowledge received (this discussion continues below). Therefore, the existence of defined and documented interaction structures between parties like Nickerson and Zenger (2004) and Blumenberg et al. (2009) suggest, is not enough. These interaction structures should be as simple as possible, and the sender must have control of the knowledge transfer process. Otherwise, the transfer of the results from one organisation to another one can turn into a game of Chinese Whispers. The receptor does not get all the information, the message is distorted, and each intermediary includes their own "touch" in the information, affecting the transfer process completely.

These findings have important implications for designing strategies to transfer knowledge in multi-organisational projects, especially when geographical separations exist among actors. If the use of intermediaries is necessary, it is important that the team coordinating the project at the lead firm considers the capabilities and internal structures of the intermediaries. Coordinators should avoid delegating overlapping responsibilities, and most importantly, the lead firm must verify if the person responsible for the intermediation has the knowledge-base to understand the information and transfer it. If there are already communication channels between the source and the receptor, as in the KINGE case, the results of this research strongly suggest avoiding the inclusion of an intermediary and opting for a direct transfer of information.

Sveiby (2001) proposed a framework at the organisational level to acquire knowledge to raise its knowledge-base and induce the creation of capabilities. In his framework,



he considered internal and external sources. He identified three levels of sources: individuals (employees), who have the “primary intangible resources”; external structures such as partners, competitors, suppliers, or others; and internal organisational structures such as repositories of explicit knowledge existing in the organisation (patents, concepts, models, and computer and administrative systems). In his framework, he assumed a direct interaction between the three sources at the intra-organisational and inter-organisational level. However, based on the evidence presented above, the presence of boundary spanners can complement this framework. A complemented framework should consider the intermediation of these boundary spanners between individuals in different organisations or between individuals and external sources of explicit information, such as external databases; sources that Sveiby’s (2001) framework did not consider and are present, as Chapter 4 showed, such as the Ministry of Health databases. With this contribution, the framework is more robust and can be employed in new scenarios such as multi-organisational projects.

### 7.3.2. Knowledge acquisition, permeability and people’s knowledge-base

The acquisition of knowledge and the task execution (Table 4) are the two components at the intra-organisational level proposed in the model. In this section, I will address the discussion about the acquisition of knowledge. The demand for knowledge and information, teams’ permeability towards external knowledge and people’s knowledge-base were three relevant elements identified in this research that mediated the knowledge acquisition.

The acquisition of knowledge in the previous models consists of the search for internal or external knowledge to implement the activities, either to increase the organisation’s “knowing” (McElroy 1999; Ngai, Jin, and Liang 2008) or to acquire data and information to be analysed or transformed into products. In these models, people already know how to process this information and data (M. H. Meyer and Zack 1996). As Gupta and Govindarajan (2000) indicated, people’s motivation to acquire and receive knowledge influences the acquisition of knowledge. However, the information presented in Chapters 4 and 5 shows that in addition to motivation, the need for the information and knowledge is a key factor that mediated the acquisition. In the case of sponsors,

they acquired knowledge and information that they needed to design the protocol (Chapter 4). And in the case of the research sites, they acquired the information and knowledge about the protocol and procedures to implement from the sponsor, the CRO or the SMOs because they needed this knowledge and information to execute the task. In both types of organisations, the permeability towards the information requested was high, and teams were open to receiving and using it to implement their productive enquiries. However, in those cases where the team did not request knowledge and information, the permeability of the teams varied and they were not always open to receiving and using the information and knowledge. This permeability varied according to the trust in the source and the valuation of the internal knowledge versus the knowledge received. Teams were less permeable if they did not request the information, they doubted the validity of the external knowledge, they did not trust the source of information, or intermediaries were filtering the information for them (Chapter 5). On the contrary, they were more open to not requested information if they trusted the source and considered the knowledge and information received as valid.

The role of trust between firms is widely acknowledged, and it has great importance in the success of inter-organisational projects (Kadefors 2004; Wong and Cheung 2004). Trust promotes the sharing of knowledge among parts, enabling the acquisition of knowledge from external partners (McEvily, Perrone, and Zaheer 2003). In previous research, Maurer (2010) concluded that in inter-organisational engineering projects trust between partners promoted knowledge acquisition. However, in their study, the association between trust and acquisition was not as strong as they expected. Therefore, they suggested that other drivers should probably be mediating the acquisition of knowledge in inter-organisational projects. The results of this PhD suggest that a combination of drivers under the concept of permeability, which includes the need for the information, the valuation of the internal knowledge versus the knowledge received and the trust in the source, can much better explain the acquisition of knowledge from external sources by the firms working on the project.

Also, the results of this research suggest that the permeability of the teams towards external sources is dynamic. This one can shift from open to close or vice-versa as trust evolves among parts over the course of the project. In the first place, if trust in the source is lost, the permeability can change from open to close. In contrast, permeability

can change from closed to open if the receptor begins to trust the source and a relationship based on trust and cooperation emerges. Then, trust can be built or can decrease among the parts as the project progressed, enabling or blocking the acquisition of knowledge. The data presented clearly indicates that the low permeability of a person towards external information or knowledge is not only associated with not-invented here syndrome (Katz and Allen 1982), in which knowledge is rejected because of envy, jealousy or power (Ngai, Jin, and Liang 2008; Maier 2004). The permeability of a person towards external information depends on:

- 1) The evaluation that the receptor conducts on the source
- 2) The experience displayed by the sender.
- 3) The experience that the receptor develops over the course of the project
- 4) The trust generated in the relationship

In summary, this work contributes to existing knowledge about the acquisition of knowledge, developing the concept of permeability. The results provide important insights into four key factors that defined the clinical team's permeability towards external knowledge and its dynamism over the course of the project. The first factor is the demand for knowledge. The second factor is the trust in the source and the validation of its knowledge. The third factor is the presence of boundary spanners-in-practice, which act as a filter that regulates the information flow among parts. And the fourth factor is the experience of people to make an informed decision about the acquisition. So, this discussion about the factors that influence the permeability of the clinical teams makes an initial contribution to the development of the concept of permeability formulated in this thesis.

This thesis considered the previous team experience or knowledge-base as one factor that influenced the acquisition of knowledge. A significant number of authors have suggested that previous knowledge (basic skills, shared language and knowledge of scientific or technological developments) modulates the potential to acquire and introduce knowledge or information in collaborative networks or outsourced activities (Li et al. 2014; Nooteboom et al. 2007; S. A. Kumar and Thangavelu 2013; Cohen and

Levinthal 1990). And it is an important condition for the recipients of information (Dwi and Alon 2017). Nonetheless, most of these discussions were oriented on understanding how the knowledge-base of individual organisations allows knowledge acquisition to be more innovative. Then, this research contributes to expanding our knowledge about the relevance of knowledge-base in multi-organisational projects where not all organisations have the same level of experience.

In multi-organisational projects, it is a fact that no organisations have the same knowledge-base and previous experience. The internal knowledge residing within the organisation and the team is unique and totally specific to the group of people at a specific point in time. And it is from these experiences that each team builds their knowledge to implement the task. The stability of project members through interlinked projects emerged as a principal element that enables the acquisition of knowledge, not only because people had the cognitive bases to translate previous experience to the new project, but also because the team had established an understanding of how to work and coordinate actions. These results are aligned with the discussion in project literature that highlights the relevance of team's stability for the project success (Savelsbergh, Poell, and van der Heijden 2015) and also facilitates coordination of interdependent work (Edmondson, Dillon, and Roloff 2007). The accumulation of specialised knowledge allows the addressing of complexities that emerge over the project (Tseng et al. 2004). The access and use of previous results are critical for its further use in interdependent projects (Formentini and Romano 2011; Owen and Burstein 2006).

In those cases where teams lack previous experience, professional backgrounds are the base to acquire knowledge and implement the task, despite the organisation to which they belong (sponsor, or research site). In these teams, knowledge acquisition is cyclic, where knowledge possessed is constantly evaluated in practice and the results can trigger learning loops if knowledge is not enough. It is the use of knowledge in practice that reveals the complete internalisation and the integration of the knowledge acquired into work (Cook and Brown 1999). Two mechanisms are employed to learn practical knowledge in multi-organisational projects. The first one is learning from example and the second one is learning by experience through a trial and error process. In the first scenario, I presented how a constant interaction with experienced staff benefited

learning (Park, Im, and Kim 2011) and the co-location of experienced personnel with inexperienced personnel enabled the acquisition of practical knowledge (Roy and Sivakumar 2012). Nonetheless, learning by experience was highly demanding and could compromise the results, especially because this learning took place over the course of the project.

Contrary to what most of the literature on knowledge management suggests about the positive role of previous knowledge on the acquisition of knowledge, the evidence presented in Chapter 5 seems to suggest that the previous knowledge is not always a catalyst to acquire new knowledge. On the contrary, the evidence presented about experienced clinicians working for the first time in clinical research showed how their previous background becomes a limitation to learn new processes and procedures to implement the task. Then, although previous knowledge allowed them to acquire new concepts and understand the project, the acquisition of new practical knowledge was complex if the person had rooted practice associated with the activity.

These findings take us to a less developed discussion about the knowledge-destruction capability that professionals must have to acquire and create new knowledge. According to Kaplan et al. (2001): "The destruction capability constitutes the capacity to eliminate elements of knowledge or disassemble the interconnectedness of knowledge." Then, to acquire new knowledge, the old one has to be destroyed and replaced by the new one. Authors like Landry et al. (2006), based on medical literature, have suggested that, for physicians, it is difficult to destroy old knowledge and replace it with new knowledge. The evidence collected in Chapters 5-6 supports this interpretation and provides qualitative evidence about the evolution of the destruction capability of physicians working in clinical trials, extending our understanding about the destruction-creation process in the acquisition of practical knowledge. Findings in Chapters 5-6 suggest that the destruction of knowledge is not a straightforward process, and not all members of research sites manifested a capability to change their previous medical practices and routines easily. In the first place, the destruction of knowledge requires that the person recognised value in the new knowledge. Secondly, destruction is a process where people introduce, day-by-day, the new knowledge into the new routines, so the old knowledge is progressively replaced with the new one. Thirdly, the person must realise the impact that the introduced knowledge has on his work. And

finally, it requires determination and motivation by the practitioner to acquire the new knowledge, and it also requires patience by the person supervising the acquisition, who has to be willing to repeat the information until the old knowledge is replaced by the new one. Therefore, these results clearly evidence that, on the acquisition of knowledge in the context of a project, previous knowledge is also destroyed to give place to the creation of new knowledge that is the result of the acquisition of the transferred knowledge and the implementation of this in the medical practice.

### 7.3.3. Use of knowledge to produce the product

At the intra-organisational level, the execution of the task is the most important part of the project. Knowledge, information and data acquired are employed to execute the activities and produce the knowledge products (M. H. Meyer and Zack 1996), give a solution to problems (McElroy 1999), or, as it will be presented, to contribute with alternative proposals. In this thesis, the use of knowledge took the approach proposed by Cook and Brown (1999), where they suggested that in the execution of productive enquiries two epistemologies of knowledge exist: the “epistemology of possession” and the “epistemology of practice”. The epistemology of possession sees knowledge as something that people have in their heads, and they can acquire and transfer it; which, in my view, is in accordance with the model this thesis proposed. The epistemology of practice is focused on what people know and do in certain contexts; this means bringing the knowledge possessed into action. Otherwise, the knowledge possessed is not contributing to people’s work. In this way, both epistemological approaches come together in work and help to explain how people employ knowledge in the productive enquiries.

I identified the knowledge, data and information employed by the research sites and the sponsor to execute the respective productive enquiries. In both scenarios, the accumulated experience/knowledge of team members was the base to execute the respective parts of the project integrated with the newly acquired knowledge. However, in knowledge-intensive projects, knowledge products are the result of the summation of the individual analytical process, where workers interrogate data, information and knowledge and create new connections to produce new knowledge. This new knowledge is then externalised in a document. However, because this process is

individualised, abstract and mental, the study of the acquired knowledge transformation is not easy. All information collected about this activity depends on the person's interpretation and narrative about its own analytical and logical process, which is a limitation to more clearly explain the creation of new knowledge by people.

The evidence also supports the argument that knowledge produced as a result of the project must be stored and lessons learned must be available to the rest of the organisation or at least for other project members (Markus 2001). The storage of knowledge has been, in part, the base of the knowledge management systems theory, whose base is the storage of the organisational knowledge to make the firm more competitive. Evidence presented in Chapter 6 indicates that research sites are not good at storing the lessons learned by workers. So, the storage of the knowledge acquired and created by the people over the course of the trial about how to execute the project is one of the weaknesses of clinical sites and the management of knowledge within these organisations.

It is important to point out that most of the previous research about the data production has studied clinical trials for chronic diseases, which are the most common in the pharmaceutical industry where recruitment is competitive between countries and physicians, and individual physicians implementing the project. Then, one of the most prominent contributions of this research is that it addresses, for the first time, the use of knowledge in the research sites and makes an in-depth analysis of how the researchers contribute with their contextual knowledge to the project. In this analysis, the need for integrating knowledge to the organisations through the standardisation of procedures and the use in practice of the knowledge acquired was evident. The integration takes place over the acquisition and use of knowledge, which makes the study of this activity harder, as it is disconnected from the other two steps. Based on the evidence presented, I argue that physicians and principal researchers in clinical sites contribute with their knowledge to the trial. They contribute not only to collecting the clinical data and transferring it to the sponsor or the CRO, but also maintaining the project's stability, and guaranteeing the enrolment and adherence of the participants over the entire project, which is fundamental for the project's success (Chapter 6).

#### 7.3.4. A conceptual model to study the knowledge flow in multi-organisational projects

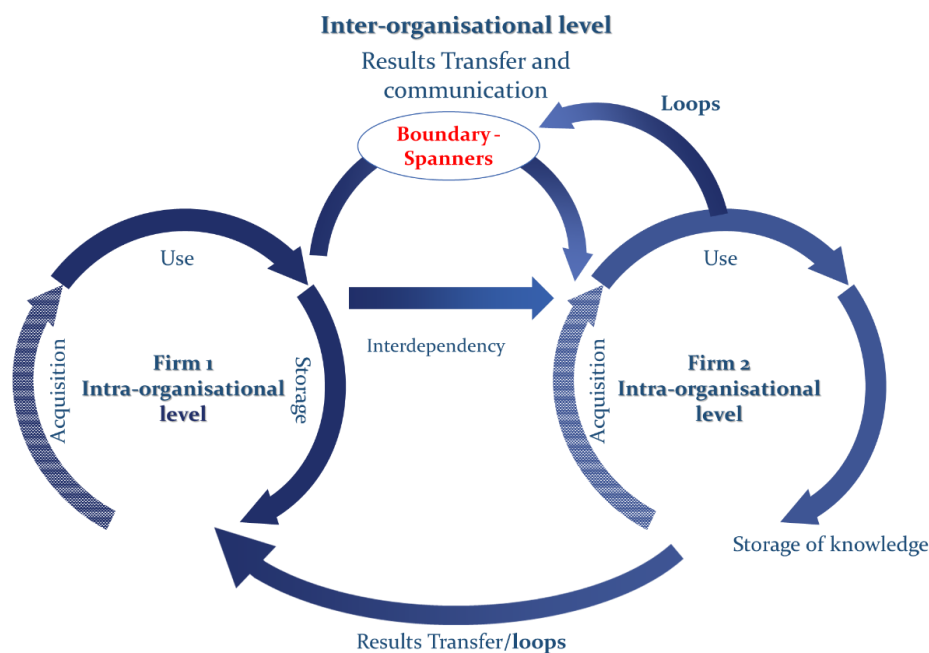
Multi-organisational projects are composed of a leading organisation and various external project teams from specialised partner firms or sub-contractors (Maurer 2010). In previous studies about inter-organisational projects such as outsourced projects, services and inter-organisational relationships, scholars had provided valuable insights into the management of knowledge. For example, they have discussed how outsourced firms create new knowledge and store it to make the firm competitive (Yan 2011; Zhao, Yim-Teo, and Yeo 2004; Matinheikki et al. 2016); how knowledge is transferred across companies; the need to create a shared knowledge among the actors (Samoilenko and Nahar 2011; A. K. Gupta and Govindarajan 2000); and the relevance of interpersonal relationships among people working on the projects (M. Jensen et al. 2007). However, despite the attention paid to the transfer of knowledge in inter-organisational projects, limited research has been conducted about the interdependency of knowledge among organisations in the project and how each one of the firms uses their internal knowledge and external knowledge to implement the tasks.

Based on the discussion in this thesis, it seems that the model proposed initially in the theoretical framework was robust to follow the flow of knowledge, data and information in different organisations participating in the project, from the design of the protocol until the production of the clinical data. However, the analysis of the data collected indicated that the model proposed can be complemented with the new evidence presented through this chapter (Figure 9). In the initial model proposed, the knowledge acquisition implies an internal-external orientation. However, in the context of multi-organisational projects, it is important to consider the perspective of the receptor, as they do not actively search for the knowledge to implement the tasks. So, considering the directionality of the acquisition is critical, especially because it affects the permeability of people towards knowledge. People were highly permeable or non-selective toward information and knowledge if they requested the information. However, they were less permeable if the information or knowledge was not demanded being reluctant to employ this knowledge in the production of the knowledge products.



Regarding learning new activities, this research has shown how the presence of strongly rooted medical routines decreases the flexibility to learn new practices, like research practices. This analysis revealed how the level of experience of researchers in medical consultation, rather than being an enabling factor to introduce the new knowledge to do clinical research, it was an obstacle. Then, the knowledge-destruction capability of people is important to acquire knowledge and should be considered as part of the factors that influence the knowledge acquisition (Figure 9). The presence of intermediaries plays an important role in modulating the transfer of knowledge among parts. The presence of boundary spanners should be considered in a model to study the knowledge flow in multi-organisational projects, either nominated boundary spanners and boundary spanners-in-practice (Levina and Vaast 2014) because, as I discussed, the delegation or emergence of these actors has a direct consequence on the flow of knowledge across interdependent actors.

**Figure 9. Complemented model to study the flow of knowledge and its use in multi-organisational projects addressing the inter-organisational level and the inter-organisational level.**



**This pattern indicates the presence of three factors influencing knowledge acquisition:**

- Previous knowledge
- Permeability
- **Knowledge-destruction capability**

Compared with other models proposed in the literature of KM, this model differs considerably on the order of the stages and, in turn, on the study of knowledge flow. For example, previous models propose that the use of knowledge is possible once this one is stored and shared in the organisation (Evans, Dalkir, and Bidian 2014). This perspective is logical in models that address the use of lessons learned in organisations, a field dominated by the literature of knowledge management systems, which analyses the use of informatics infrastructure to manage the knowledge in organisations. However, the model proposed aim to address dynamics at the inter-organisational level, where knowledge acquisition and use takes place before storing and sharing lessons learned, offering a different starting point to study knowledge management in the organisations.

So, in this section, I discuss the pertinence of the model proposed to study the chain of interaction and dependencies that take place in multi-organisational projects, discussing step-by-step the steps proposed. In conclusion, I present several noteworthy contributions that this study makes to the field of knowledge management, specifically to the literature of knowledge models and the studies of outsourced project or services. First, proposing a model that brings together the intra-organisational and inter-organisational dimension of the knowledge flow and simultaneously presents the transformation of the knowledge in different interdependent knowledge products. And secondly, evaluating and complementing the proposed model.

## 7.4. Conclusions, shortcomings of the work and avenues for further work

This is the first study to undertake a longitudinal analysis of knowledge management in multi-organisational projects, advancing our understanding about the flow and use of knowledge in this kind of project. The study offers some important insights into the knowledge management at the inter-organisational level and intra-organisational level in these projects. In this thesis, I highlighted the lack of a model to study and map the flow of knowledge over the course of a multi-organisational project, addressing its implications for theory and practice. This study aimed to contribute to this growing area of research by elaborating a conceptual model to study the flow of knowledge, and its use across organisations that participate in KIP and are working on outsourcing KIP.

The proposed model was evaluated and complemented based on the evidence collected from three multi-organisational projects to evaluate vaccine candidates in Colombia, Brazil and Mexico. The analysis of the results allowed me to complement the model initially proposed and also allowed me to expand my own knowledge of how knowledge, data and information flow and are used to produce knowledge products through interdependent productive enquiries. This study has shown that knowledge flow across the organisation is not direct and linear. The results of this study indicate that the presence of intermediaries, the permeability of receptors and integration of knowledge in practice are fundamental not only to ensure knowledge flow but also to transform knowledge into knowledge products, such as boundary objects. This study proposes and elaborates on the concept of permeability increasing the understanding of the knowledge acquisition in teams and organisations. The insights gained provide researchers and clinical trial practitioners with valuable understanding about how clinical trials in a new fragmented landscape are developed in Latin America, where the presence of intermediaries is highly relevant to manage clinical trials. So, this research extends our knowledge about clinical trials in Latin America; a topic under-studied until now. Nonetheless, more research in other contexts employing the proposed model is required to determine its applicability in other contexts.

Due to practical constraints to gain access to biological laboratories where sponsors implemented blood tests, and to statistical teams, this research cannot provide a comprehensive review about the production of biological data and the integration of this data with the clinical data to obtain the final results. For this reason, analysis and conclusions are limited to the production of clinical data and its review by the sponsor. A further study with more focus on the participation of these actors is therefore suggested to comprehend how sponsors analysed and refined data collected by sites and the biological data to have a whole picture of the clinical trials.

In this research, I pointed out the relevance of the knowledge that research sites had about the communities. However, I consider it relevant to explore the understanding that communities have about the projects and their responsibilities for it. As I presented, rumours emerged in a clinical trial, and some communities created their own collective perception of the project and the procedures. Therefore, learning how communities generated these perceptions became relevant to address at the planning

stages of large clinical trials. Moreover, in Mexico in one of the clinical trial industry conventions, I witnessed how some volunteers publicly showed a low understanding of their rights if they experienced associated side effects. So, further research needs to more closely examine the transfer of knowledge to participants and its understanding by volunteers, as the acquisition of knowledge by people has direct implications for participants' health and claiming of their rights.

I consider it relevant to address, in future research, the transfer of knowledge, not only clinical data, from the research sites to the sponsor. Research sites develop a rich understanding of clinical research and a profound practical knowledge that can benefit the sponsor in the planning and execution of future research. Then, in the transfer of lessons learned from the site to the sponsor, there is a potential to gain knowledge that has been unexplored by sponsor companies and future research should address this. The translation of results in this research to other multi-organisational projects, even clinical trials for chronic diseases, should be with caution, because in these last cases trials are not outsourced to research sites; they are outsourced to individual practitioners, which changes the dynamic in the project and the work of the CRO is much more relevant. A natural progression of this work is to compare results of multi-organisational projects in multiple fields to determine the robustness of the proposed model in multiple research contexts.

Although I collected data about the clinical trial industry in Colombia, Brazil and Mexico, the current research was not specifically designed to evaluate factors related to knowledge production in the entire clinical trial industry in the three countries. The constant reshaping of local regulations was beyond the scope of this study, which had a project level. Then, future research derived from this work can investigate the results of the regulatory changes on the quality of the clinical research, its influence on the project execution and the industry dynamic, passing from a project level to an industry level in Latin America.

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# Appendix

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## Appendix 1.

### Questions to the Sponsor

**1. Interviewed personal details**

Can you tell me about your academic background?  
For how long have you been working in the institution?  
What are your core responsibilities here in the company?

**2. Project planning**

Who designed the protocol?  
What is the criteria to select the outsourced companies?  
Could you explain me, how is the process to you agree a contract with other organisations?  
Did any regulatory authority participate/contribute to the protocol design?

**3. Transition stage**

How was the process to implement the protocol in each centre?  
What information did you transfer to the site? Did you train staff? How did you do it?  
How do you make explicit to the research group the type of data that you need to produce?  
How do you guarantee that all procedures are standardised?  
How do you ensure reproducibility of the results among research groups?  
Did you visit the research site?

**4. Control over the project**

What channels of communication do you establish with the group to follow up the progress?  
Can you monitor the progression of the trial in real time?  
Do you use some metrics such as patient enrolment to evaluate the contribution of the research group to the project?  
Is the language a barrier in the clinical trials?

**5. Data integration**

Once recruiting is taking place and data is produced, how do you compile that information?  
How do you ensure that data and information is protected?  
Can you describe to me how the process of integrating data coming from different centres or countries has been for your company?

**6. Offshoring of clinical trials**

Which ones are the main barriers that you find to conduct the trial in collaboration with other organisations?  
 Have you noticed that some organisational culture or local culture practices have an effect over the clinical trial?  
 How do research sites manage the production of data under the context of transnational offshored clinical trials?

## Question to personnel in the site

### 1. **Research site background**

Can you tell me a bit about your background as a researcher?  
 For how long have you been conducting clinical research?  
 What are the main areas of research in your research group?  
 Why did you start to conduct clinical trials?  
 Who is responsible for obtaining the ethical approval to conduct the trial?

### 2. **Knowledge transfer**

What technical information do you receive from the PC before starting the trial?  
 How are the people who are going to conduct the trial trained?  
 Once you receive the protocol, who has access to it?  
 Do you receive formularies and informed concerns by the PC?  
 Is there a process to standardise the production data among different research groups?  
 What other kind of information do you receive from the pharmaceutical company/CRO?  
 To conduct new clinical trials, do you hire new people or try to employ students or researchers that have been working with you?

### 3. **Implementing the trial**

What agreements were made with other institutions to access patients?  
 How is the process to follow up the patients?  
 Can you tell me, how is the routine to implement the protocol? What do you evaluate? Who produces the data?  
 How easy/complex is it to implement the protocol?  
 How do you protect the new information generated?  
 Do you consider that conducting clinical trials have impacted other areas of research? In what way?  
 Beside the protocol transferred by the PC, what other regulations should you consider when conducting research?

### 4. **Data transfer/storage**

When a person that has been working on a project leaves, how do you store the knowledge that the person has?  
 Do you have a strategy to generate a back-up of data and results in the lab?  
 How do you transmit the information to the pharmaceutical company? Do you have software to share data?  
 How often do you have communication with the PC?  
 Do you perceive any kind of control by the PCs? In what way?

**5. Results**

How is a vaccine's safety, efficacy and efficiency determined?

Are you allowed to process your own data?

How do you corroborate the consistency of your data?

Do you have access to results obtained in other settings?

## Appendix 2.

List of interviews transcribed and codes employed to quote the references.

Reference	Pseudonym	Interview date	Responsibility	Country	City	Case of Study
[DM-USP, NUSTAN, Apr-13-2015]	Leonardo Silva	Abril 13 2015	Data Manager	Brazil	Sao Paulo	NUSTAN
[Monitor-CRO, KINGE-Col Nov-27-2014]	Silvia Martinez	Nov 27 2014	CRO	Colombia	Medellín	KINGE
[Monitor-CRO, SAVA-Col Dic-10-2014]	Pablo Montes	Dic 10 2014	CRO	Colombia	Armenia	SAVA
[Monitor-CRO, SAVA-Mex, Jul-08-2015]		Julio 8 2015	CRO	Mexico	Tizimi- Yucatan	SAVA
[NUSTAN Chair, Apr-13-2017]	Dr. Pablo Esmeralda	Abril 13 2015	Sponsor	Brazil	Sao Paulo	SAVA
[OM SMO-2, SAVA-Col, Dic-03-2014]	Manuela Figueroa	Dic 03 2014	Project manager	Colombia	Bogotá	SAVA
[PI 1-Site2, SMO-3, SAVA-Mex, May-15-2015]	Dr. Javier Rubi	Mayo 15 2015	Principal Investigator	Mexico	Ciudad de México	SAVA
[PI 2-Site2, SMO-3, SAVA-Mex, Jul-01-2015]	GP Sofia Villareal	Julio 1 2015	Sub- Researcher	Mexico	Temixco	SAVA
[PI- R-IDVI, KINGE, Oct-15-2014]	Dr. Ignacio Valdivia	Oct 15 2014	Principal Investigator	Colombia	Medellín	KINGE
[PI Site3, SAVA-Mex, Jul-08-2015]	Dr. Gabriel Valderrama	Julio 8 2015	Principal Investigator	Mexico	Tizimi- Yucatan	SAVA
[PI-Site 4, SMO-3, SAVA-Mex, Jul-09-2015]	Dr Maria Cristina Macias	Julio 9 2015	Principal Investigator	Mexico	Valladolid	SAVA
[PI-Site-1, SMO-1, SAVA-Col, Dic-10-2014]	Dr. Augusto Perla	Dic 10 2014	Principal Investigator	Colombia	Armenia	SAVA
[PI-SMO-1, SAVA-Col, Dic-02-2014]	Dr. Roberto Cristales	Dec 02 2014	SMO	Colombia	Bogotá	SAVA
[PI-SMO-2, SAVA-Col, May-17-2015]	Dr. Horacio Espinela	Mar 17 2015	SMO	Colombia	Bogotá	SAVA
[PI-SMO-3, SAVA-Mex, Jun-24-2015]	Dr. Jorge Ágata	June 24 2015	SMO	Mexico	Ciudad de México	SAVA
[PI-USP, NUSTA, Apr-01-2015]	Dr. João Espinela	April 1 2015	Principal Investigator	Brazil	Sao Paulo	NUSTAN
[PM R-IDVI, KINGE, Nov-05-2014]	Leonora Opalo	Nov 05 2014	Project manager	Colombia	Medellín	KINGE
[PM2 R-IDVI, KINGE, Nov-05-2014]		Oct 22 2014	Project manager	Colombia	Medellín	KINGE
[PM-Site-1, SMO-1, SAVA-Col, Dic-10-2014]	Luz Elena Nuñez	Dic 10 2014	Project manager	Colombia	Armenia	SAVA

[PM-Site-4, SMO-3, SAVA-Mex, Jul-09-2015]	Paloma Abán	Julio 9 2015	Project manager	Mexico	Valladolid	SAVA
[PM-USP, NUSTA, Apr-01-2015]	Laura Ferreyra	April 1 2015	Project manager	Brazil	Sao Paulo	NUSTAN
[PQ R-IDVI, KINGE, Nov-06-2014]	Natalia Topacio	Nov 06 2014	Pharmaceutical chemistry	Colombia	Medellín	KINGE
[QA, R-IDVI, KINGE, Nov-11-2014]	Emilia Coral	Nov 11 2014	Quality Manager	Colombia	Medellín	KINGE
[Rep-Health secretary Antioquia, Feb-10-2015]		Feb 10 2015	Health Secretary	Colombia	Medellín	Health Secretary Antioquia
[SAVA Sponsor Brz, Apr-10-2015]	Wallace Coutinho	Abril 10 2015	Sponsor	Brazil	Sao Paulo	SAVA
[SAVA Sponsor Mex, May-07-2015]	Fernando Amatista	Mayo 7 2015	Sponsor	Mexico	Ciudad de México	SAVA
[SAVA-Sponsor Col, Mar-24-2015]	Ana Diamante	Mar 24 2015	Sponsor	Colombia	Bogotá	SAVA
[Sponsor- KINGE, Oct-25-2014]	Dr. Jaime Plata	Oct 25 2014	Sponsor	Colombia	Medellín	KINGE
[Sub-Res, R-IDVI, KINGE, Nov-05-2014]	GP David Vega	Nov 05 2014	Sub- Researcher	Colombia	Medellín	KINGE
[Sub-Res, Site-3, SMO-3, SAVA-Mex, Jul-08-2015]	Dr Camilo Miranda	Julio 8 2015	Sub- Researcher	Mexico	Tizimi- Yucatan	SAVA
[Sub-Res-Site 4, SMO-3, SAVA-Mex, Jul-09-2015]	William Arango	Julio 9 2015	Sub- Researcher	Mexico	Valladolid	SAVA
[Sub-Res-Site2, SMO-3, SAVA-Mex, May-15-2015]	Felipe Rojas	Julio 1 2015	Sub- Researcher	Mexico	Taltizaplan	SAVA
[Sub-Res-USP, NUSTA, Apr-14-2015]	Dr. Rodrigo Coutinho	Abril 14 2015	Sub- Researcher	Brazil	Sao Paulo	NUSTAN
[SW-Site 4, SMO-3, SAVA-Mex, Jul-09-2015]	Alberto Congote	Julio 9 2016	Social Worker	Mexico	Valladolid	SAVA
[SW-Site4, SMO-3, SAVA-Mex, Jul-09-2015]	Maria Luisa Tobar	Julio 9 2015	Social Worker	Mexico	Valladolid	SAVA
Nurse-Site4, SMO-3, SAVA-Mex, Jul-09-2015]		Julio 9 2015	Nurse	Mexico	Valladolid	SAVA
		Nov 05 2014	Ethic committee secretary	Colombia	Medellín	KINGE
		Julio 9 2015	Health Promoter	Mexico	Valladolid	SAVA
		Julio 9 2015	Health Promoter	Mexico	Valladolid	SAVA
		Nov 18 2014	Informatic coordinator	Colombia	Medellín	KINGE

		Mar 19 2015	INVIMA	Colombia	Bogotá	Colombian Regulation
		Julio 9 2015	Laboratory Technician	Mexico	Valladolid	SAVA
		Julio 9 2015	Nurse	Mexico	Valladolid	SAVA
		Julio 9 2015	Nurse	Mexico	Valladolid	SAVA
		Dic 03 2014	Principal Investigator		Bogotá	SAVA
		Dic 04 2014	Principal Investigator		Bogotá	SAVA
		Abril 15 2015	Seminar in Brazil	Brazil	Brasilia	Brasilian Regulation
		May 21-22 2015	Seminar in Mexico	Mexico	Ciudad de México	Mexican associations
		Julio 9 2015	Social Worker	Mexico	Valladolid	SAVA
		Abril 20 2015	Sub- Researcher	Brazil	Recife	SAVA
		Julio 9 2015	Sub- Researcher	Mexico	Valladolid	SAVA

## Appendix 3.

### Introductory letter to request interviews

Medellín, Colombia 6th March 2015

Dear

My name is Sara Valencia Cadavid and I'm a PhD candidate at the programme of Science and Technology Studies at the University of Edinburgh. Right now, I'm conducting an academic research to identify how knowledge is employed and flows in multi-centric clinical trials to evaluate vaccines in Colombia, Brazil and Mexico.

The Instituto XXX has been conducting a multi-centric clinical trial to evaluate a XXXX vaccine candidate in Brazil. And for this reason, I would like to have an academic interview with you, to know more about your experience sponsoring a clinical trial, how is your relationship with the research sites, what challenges have you faced on the project design and how you have overcome challenges. All information that you will provide is confidential and it will be used just with academic purposes.

I will travel to Brazil and I really appreciate if I can interview you at the day and time that best suits you between March 26th and April 4th. The length of the interview is between 30 minutes and one hour.

If you have any questions, don't hesitate to contact me; I will be glad to answer your questions.

## Appendix 4.

### Informed consent in English

All people quoted in this thesis signed this confidential form either in Spanish or in Portuguese.

The data obtained during the interview conducted by the researcher Sara Valencia will be used only for the research project to which she aspires to the title of Doctor of Science and Technology Studies at the University of Edinburgh in Scotland.

All information provided will be recorded and it is confidential unless you explicitly authorize the publication of your name or your organisation's name. The confidentiality agreement means that none of your personal or organizational data will appear or be used in reports, thesis and other publications, including, but not limited to, journal articles and book chapters.

Regarding the information provided, I declare that:

1. My participation is completely voluntary and it is my decision.
2. I have read and understood the information about the project that I have been given, and I have been able to discuss it with the researcher.
3. I will not receive financial compensation for participating in the project.
4. I have understood that the interview will be recorded unless I have an objection.
5. I understand that specific parts of the conversation may be used for the report and/or future publications but my name will be kept confidential.
6. I have had the opportunity to discuss this study and ask questions.

I, \_\_\_\_\_ agree to be interviewed by Sara Marcela Valencia Cadavid for academic purposes in her PhD research.

I authorize the use of my name in the material published based on the information I provided.

Yes ☐ No ☐

Signature \_\_\_\_\_ Date \_\_\_\_\_